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<p>(54) Title: AMIDES AS NPY5 RECEPTOR ANTAGONISTS</p> <p>(57) Abstract</p> <p>α-alkoxy and α-thioalkoxyamide compounds of formula (I) and methods of administering the compositions to mammals to treat disorders such as obesity that are mediated by NPY and especially those mediated by NPY via the Y5 receptor, or pharmaceutically acceptable salts thereof wherein R₁-R₅ are each individually selected from the group of substituents including hydrogen, halogen, hydroxyl, thiol, lower alkyl, substituted lower alkyl, alkenyl, alkynyl, alkylalkenyl, alkylalkynyl, alkoxy, alkylthio, acyl, aryloxy, amino, amido, carboxyl, aryl, substituted aryl, heterocycle, heteroaryl, substituted heterocycle, heteroalkyl, cycloalkyl, substituted cycloalkyl, alkylcycloalkyl, alkylcycloheteroalkyl, phenyl, substituted phenyl, benzothiophene, furan, fluoride, nitro, cyano, naphthyl, substituted naphthyl, fluorene, substituted fluorene and dibenzofuran, and wherein X is oxygen or sulfur.</p>		

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AMIDES AS NPY5 RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

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1) Field of the Invention

This invention is a method for inhibiting the neuropeptide Y ("NPY") Y5 receptor using a class of substituted α -alkoxy and α -thioalkoxyamide compositions. As antagonists of the Y5 receptor, the compositions are useful in treating obese mammals, mammals with bulimia, for treating mammals with obesity related disorders including, but not limited to type II diabetes, insulin resistance, hyperlipidemia, hypertension, polycystic ovarian disease, pulmonary disease, sleep apnea, and for treating mammals suffering from NPY Y5 receptor inhibition related disorders such as memory disorders, epilepsy, dyslipidemia, and depression.

15 (2) Description of the Art

NPY is a 36 amino acid peptide that is a member of a larger peptide family which includes peptide YY (PYY), and pancreatic peptide (PP). NPY is highly conserved in a variety of animal, reptile and fish species and is found mainly in the central and peripheral sympathetic neurons. Furthermore, NPY is the most prevalent peptide in the mammalian brain where it is found primarily in the limbic regions. NPY has been found to elicit a number of physiological responses including appetite stimulation, anxiolysis, hypertension, and regulation of coronary tone.

NPY is believed to stimulate food intake by activating a hypothalamic eating receptor. Hu et al., J. Bio. Chem., Vol. 271, No. 42 pp.26315-319 (1996) discloses the isolation and identification and the expression cloning of a novel Y-type receptor from rat hypothalamus which the authors designated Y5. According to Hu et al., the localization of

Y5 mRNA in critical areas of the brain hypothalamus and other brain regions known to regulate food intake together with an *in vitro* pharmacological profile consistent with the *in vivo* feeding data leads those skilled in the art to believe that the Y5 receptor is a primary mediator of NPY-induced feeding. A human homologue of the Y5 receptor has also been
5 identified by Gerald et al., Nature, 382:168-171 (1996) which discloses the isolation, expression and analysis of an NPY Y5 receptor from the rat hypothalamus.

Antagonists of NPY receptors other than the Y5 receptors have been identified. For example, U.S. Patent No. 5,554,621 discloses NPY antagonists that act on the Y1, Y2, Y3 and other Y1-like or Y4-type receptors. The reported antagonists are dihydropyridine based
10 substituents.

U.S. Patent No. 5,506,248 also discloses NPY receptor antagonists. The compositions disclosed each include sulphamadyl and amidino radicals. The disclosed compositions do not include sulfur or oxygen in the backbone structure.

WO 96/16542 discloses genetically modified NPY receptors.

15 There is evidence that the Y5 receptor of NPY has a pharmacological feeding profile that is unique in comparison to other NPY receptors, namely, Y1, Y2, Y3 and Y4/PP1 because the Y5 receptor response correlates well with *in vivo* potencies of the standard peptides in the stimulation of feeding. Furthermore, antagonists of other NPY receptors such as Y1 do not necessarily exhibit an inhibitory response when assayed against Y5. In
20 view of the knowledge that NPY plays an important role in eating and other disorders and in view of the knowledge that the Y5 receptor plays an important and unique role in the mechanism of such disorders, there is, therefore, a great need for antagonists of the NPY Y5 receptor. Furthermore, there is a need for antagonists of NPY that specifically target the Y5 receptor.

SUMMARY OF THE INVENTION

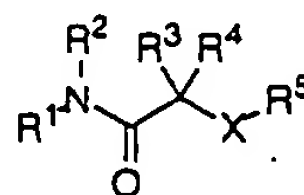
It is an object of this invention to provide a method for treating obesity, obesity related disorders and eating disorders in mammals using a therapeutically effective amount of a composition heretofore unknown for its NPY Y5 inhibitory properties.

5 It is another object of this invention to provide a method for the effective treatment of diseases in mammals that include the NPY Y5 receptor in their mechanism.

It is still another object of this invention to provide a method for the treatment of obesity and bulimia in humans using a class of substituted α -alkoxy and α -thioalkoxyamide compositions.

10 Another object of this invention are novel α -alkoxy and α -thioalkoxyamide compositions that are useful as NPY Y5 receptor antagonists and therapeutic compositions containing the same.

In one embodiment, this invention is a method for treating mammalian disorders mediated by the NPY Y5 receptor comprising the administration to a mammal of a
15 therapeutically effective amount of at least one compound having the formula:



or pharmaceutically acceptable salts thereof wherein R₁-R₅ are each individually selected from the group of substituents including hydrogen, halogen, hydroxyl, thiol, lower alkyl, substituted lower alkyl, alkenyl, alkynyl, alkylalkenyl, alkyl alkynyl, alkoxy, alkylthio,
20 acyl, aryloxy, amino, amido, carboxyl, aryl, substituted aryl, heterocycle, heteroaryl, substituted heterocycle, heteroalkyl, cycloalkyl, substituted cycloalkyl, alkylcycloalkyl, alkylcycloheteroalkyl, nitro, phenyl, substituted phenyl, benzothiophene, furan, fluoride,

cyano, naphthyl, substituted naphthyl, fluorene, substituted fluorene and dibenzofuran and X is oxygen or sulfur.

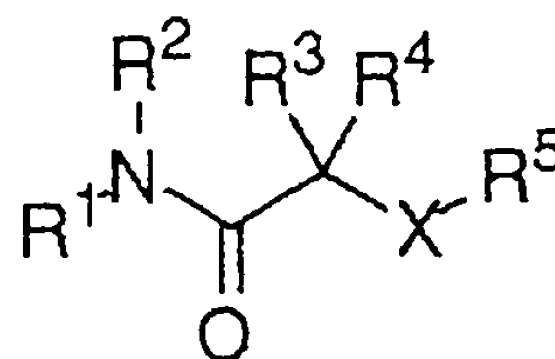
In another embodiment, this invention is a class of novel α -alkoxy and α -thioalkoxyamide compositions. The novel compositions have the same general formula disclosed above except for compounds 137-188 identified in Table 4 as prior art compositions.

In yet another embodiment, this invention is a pharmaceutical dosage form comprising the novel α -alkoxy and α -thioalkoxyamide compositions described above and at least one pharmaceutical additive.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to methods for using α -alkoxy and α -thioalkoxyamide compositions that are NPY Y5 receptor antagonists to treat NPY mediated disorders including eating disorders such as bulimia and obesity. The present invention also includes
5 novel α -alkoxy and α -thioalkoxyamide compositions. The α -alkoxy and α -thioalkoxyamide compositions described immediately below, except for compounds 137-188 disclosed in Table 4 are novel, while the compounds described below, including compounds 137-188 disclosed in Table 4 are useful in the methods disclosed herein.

Compositions that fall within the scope of this invention have the general formula:



10

wherein R¹-R⁵ are each individually selected from the group of substituents including hydrogen, halogen, hydroxyl, thiol, lower alkyl, substituted lower alkyl, alkenyl, alkynyl, alkylalkenyl, alkyl alkynyl, alkoxy, alkylthio, acyl, aryloxy, amino, amido, carboxyl, aryl, substituted aryl, heterocycle, heteroaryl, substituted heterocycle, heteroalkyl,
15 cycloalkyl, substituted cycloalkyl, alkylcycloalkyl, alkylcycloheteroalkyl, phenyl, substituted phenyl, benzothiophene, furan, fluoride, nitro, cyano, naphthyl, substituted naphthyl, fluorene, substituted fluorene and dibenzofuran and wherein X is sulfur, or oxygen.

In the novel compositions of this invention, R¹ may be any substituent other than
20 those R¹ substituents used in compounds 137-188 as disclosed in Table 4. More preferably,

in the novel compounds of this invention, R^1 will be selected from the group of substituents including lower alkyl, substituted lower alkyl, substituted phenyl, phenyl, benzothiophene, furan, naphthyl, substituted naphthyl, fluorene, substituted fluorene, dibenzofuran and fluorine. When R^1 is a substituted phenyl, then the substituted phenyl may be substituted
5 with one or more substituents including phenyl, cyanophenyl, halogens including fluoride, chloride, iodide and bromide, a branched or straight chain alkyl group having from 1 to 6 carbon atoms.

It is preferred that R^2 is hydrogen, or an unsubstituted or substituted alkyl group having from 1 to 6 carbon atoms.

10 R^1 and R^2 can together with an adjacent nitrogen atom form a 3 atom to 7 atom heterocycle.

It is preferred that R^3 and R^4 are individually selected from the group hydrogen, lower alkyl, substituted lower alkyl, or substituted or unsubstituted phenyl. R^3 and R^4 are more preferably each individually selected from the group hydrogen, substituted or
15 unsubstituted phenyl, alkyl, or substituted alkyl wherein the substituted alkyl is substituted with one or more groups having from 1 to 6 carbon atoms. R^3 and R^4 are most preferably hydrogen, $-CH_3$, or phenyl that is optionally substituted with halogen, an alkoxy having from 1 to 6 carbon atoms, or an alkyl group having from 1 to 6 carbon atoms.

It is preferred that R^5 is a lower alkyl; a substituted lower alkyl wherein the
20 substituted lower alkyl may be substituted with one or more substituents selected from the group including hydroxyl, mercaptomethylphenyl, furan, and phenyl substituted up to three times with a methyl group; N-methylpiperidine; phenyl optionally substituted with a lower alkyl group, alkoxy, thioalkoxy, amino, aminoacyl, hydroxyl or fluoro group; pyridine; pyridine N-oxide; unsubstituted pyrimidine; pyrimidine substituted with from one to three

substituents selected from the group including lower alkyl, hydroxyl, nitroso, amino, trifluoromethyl, and thiol; 1,3,5-triazine substituted up to two times with amino, thiol, or a mixture thereof; 4,5-dihydrothiazole; phenyl substituted 1,2,4-oxadiazole; 1,3,4-oxadiazole substituted with phenyl or with 2,4-dichlorophenoxyethyl; 1,3,4-thiadiazole substituted with amino, an aminoalkyl group having from 1 to 6 carbon atoms, and with lower alkyl; unsubstituted imidazole; imidazole that is substituted with one or more substituents including lower alkyl, phenyl, chloride substituted phenyl, hydroxymethyl, carboalkoxy, and mixtures thereof; 4,5-dihydroimidazole; lower alkyl substituted 4, 5-dihydroimidazole; 1,2,4-triazole; 1, 2, 4-triazole that is mono-substituted or bi-substituted with lower alkyl, unsubstituted thiazole, thiazole that is mono-substituted or bi-substituted with lower alkyl or 5-methylisoxazole thereof, lower alkyl substituted isoxazole, furan, unsubstituted imidazole, imidazole that is substituted with one or more substituents including lower alkyl, thioalkoxy, thiophenylsulfanylmethyl, thiophenylmethyl, 4-methyl-5-(3-methylsulfanyl-6; 7-dihydrobenzo[c]thiophene), unsubstituted pyridine, pyridine that is substituted with one or more substituents including alkoxy, chloride, trifluoromethyl or mixtures thereof, amino, trifluoromethyl, unsubstituted phenyl, phenyl that is substituted with alkoxy, chloride, trifluoromethyl and mixtures thereof, 2, 2-dimethoxyethyl, 2-oxo-5-trifluormethyl-2H-pyridin-1-methyl or hydroxy; 3-fluorophenyl substituted 5-oxo-1, 2, 4 triazole; unsubstituted tetrazole; tetrazole substituted with lower alkyl, phenyl, or hydroxy substituted phenyl; unsubstituted benzoimidazole; benzoimidazole that is substituted with one or more substituents including lower alkyl, alkoxy, nitro, trifluoromethyl, and mixtures thereof; unsubstituted benzothiazole; benzothiazole that is substituted with alkoxy or chloride; benzooxazole; unsubstituted pyrazolo[3,4-d]pyrimidin; amine substituted pyrazolo[3,4-d]pyrimidin; 1,2,4-triazolo[1,5a]pyrimidine; amine substituted 1,2,4-

triazolo[1,5a]pyrimidine; 1,2,4-triazolo[1,5a]pyrimidine bi-substituted with unsubstituted or substituted lower alkyl or bi-substituted with unsubstituted or substituted pyridine that when substituted is mono- or bi-substituted with amine, hydroxy, 3, 4-dihydroxy-5-hydroxymethyltetrahydrofuran, or mixtures thereof; 4-oxo-3, 4-dihydroquinazoline; 5 quinazoline; quinoline; and trifluoromethyl substituted quinoline.

The following definitions apply to certain terms used herein.

The term "halogen" refers to fluorine, bromine, chlorine, and iodine atoms.

The term "hydroxyl" refers to the group -OH.

The term "furan" refers to a five membered oxygen containing saturated or 10 unsaturated heterocycle.

The term "oxo" refers to the group =O.

The terms "thiol" and "mercapto" refers to the groups -SH, and -S(O)₀₋₂, respectively.

The term "lower alkyl" refers to a cyclic, branched, or straight chain alkyl group of 15 one to ten carbon atoms. This term is further exemplified by such groups as methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, i-butyl (or 2-methylpropyl), cyclopropylmethyl, i-amyl, n-amyl, hexyl and the like.

The term "substituted lower alkyl" refers to lower alkyl as just described including one or more substituents such as hydroxyl, thiol, alkylthiol, halogen, alkoxy, amino, amido, 20 carboxyl, cycloalkyl, substituted cycloalkyl, heterocycle, cycloheteroalkyl, substituted cycloheteroalkyl, acyl, carboxyl, aryl, substituted aryl, aryloxy, heteroaryl, substituted heteroaryl, arylalkyl, heteroarylalkyl, alkyl alkenyl, alkyl alkynyl, alkyl cycloalkyl, alkyl cycloheteroalkyl, and cyano. These groups may be attached to any carbon atom of the lower alkyl moiety.

The term "alkenyl" refers to a group $-R'C=CR''R'''$ where R' , R'' , R''' are each individually selected from hydrogen, halogen, lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or the like.

The term "alkynyl" refers to a group $-C\equiv C-R'$; where R' is selected from
5 hydrogen, halogen, lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or the like.

The term "alkyl alkenyl" refers to a group $-R-CR'=CR''R'''$, where R is lower alkyl, or substituted lower alkyl, R' , R'' , R''' are each independently selected from hydrogen, halogen, lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl,
10 heteroaryl, or substituted heteroaryl.

The term "alkyl alkynyl" refers to a group $-RC\equiv CR'$ where R is lower alkyl or substituted lower alkyl, R' is hydrogen, lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl.

The term "alkoxy" refers to the group $-OR$, where R is lower alkyl, substituted lower
15 alkyl, acyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, or substituted cycloheteroalkyl.

The term "alkylthio" denotes the group $-SR$, $-S(O)_{n-1,2}-R$, where R is lower alkyl, substituted lower alkyl, aryl, substituted aryl, arylalkyl or substituted arylalkyl.

The term "acyl" refers to groups $-C(O)R$, where R is hydrogen, lower alkyl,
20 substituted lower alkyl, aryl, substituted aryl and the like.

The term "aryloxy" refers to groups $-OAr$, where Ar is an aryl, substituted aryl, heteroaryl, or substituted heteroaryl group.

The term "amino" refers to the group NRR' , where R and R' may independently be hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl,

heteroaryl, cycloalkyl, substituted heteroaryl, or acyl.

The term "amido" refers to the group $-C(O)NRR'$, where R and R' may independently be hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl.

5 The term "carboxyl" refers to the group $-C(O)OR$, where R may independently be hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl and the like.

The terms "aryl" and "Ar" refer to an aromatic carbocyclic group having at least one aromatic ring (e.g., phenyl or biphenyl) or multiple condensed rings in which at least one
10 ring is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl, anthryl, or phenanthryl).

The term "substituted aryl" refers to aryl optionally substituted with one or more functional groups, e.g., halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, heteroaryl, substituted heteroaryl, nitro, cyano, alkylthio, thiol, sulfamido and the like.

15 The term "heterocycle" refers to a saturated, unsaturated, or aromatic carbocyclic group having a single ring (e.g., morpholino, pyridyl or furyl) or multiple condensed rings (e.g., naphthpyridyl, quinoxalyl, quinolinyl, indolizinyll or benzo[b]thienyl) and having at least one hetero atom, such as N, O, or S, within the ring, which can optionally be unsubstituted or substituted with, e.g., halogen, lower alkyl, alkoxy, lower alkylthio,
20 trifluoromethyl, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, heteroaryl, substituted heteroaryl, nitro, cyano, alkylthio, thiol, sulfamido and the like.

The term "heteroaryl" refers to a heterocycle in which at least one heterocyclic ring is aromatic.

The term "substituted heteroaryl" refers to a heterocycle optionally substituted with one or more substituents including halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, heteroaryl, substituted heteroaryl, nitro, cyano, alkylthio, thiol, sulfamido and the like.

5 The term "arylalkyl" refers to the group -R-Ar where Ar is an aryl group and R is lower alkyl or substituted lower alkyl group. Aryl groups can optionally be unsubstituted or substituted with, e.g., halogen, lower alkyl, alkoxy, alkylthio, trifluoromethyl, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, heteroaryl, substituted heteroaryl, nitro, cyano, thiol, sulfamido and the like.

10 The term "heteroalkyl" refers to the group -R-Het where Het is a heterocycle group and R is a lower alkyl group. Heteroalkyl groups can optionally be unsubstituted or substituted with e.g., halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, heteroaryl, substituted heteroaryl, nitro, cyano, alkylthio, thiol, sulfamido and the like.

15 The term "heteroarylalkyl" refers to the group -R-HetAr where HetAr is a heteroaryl group and R is a lower alkyl or substituted lower alkyl. Heteroarylalkyl groups can optionally be unsubstituted or substituted with, e.g., halogen, lower alkyl, substituted lower alkyl, alkoxy, alkylthio, aryl, aryloxy, heterocycle, heteroaryl, substituted heteroaryl, nitro, cyano, alkylthio, thiol, sulfamido and the like.

20 The term "cycloalkyl" refers to a divalent cyclic or polycyclic alkyl group containing 3 to 15 carbons. For polycyclic groups, these may be multiple condensed rings in which one of the distal rings may be aromatic (e.g., indanyl, tetrahydronaphthalene, etc. . . .).

The term "substituted cycloalkyl" refers to a cycloalkyl group comprising one or more substituents with, e.g., halogen, lower alkyl, substituted lower alkyl, alkoxy, alkylthio,

aryl, aryloxy, heterocycle, heteroaryl, substituted heteroaryl, nitro, cyano, alkylthio, thiol, sulfamido and the like.

The term "cycloheteroalkyl" refers to a cycloalkyl group wherein one or more of the ring carbon atoms is replaced with a heteroatom (e.g., N, O, S or P).

5 The term "substituted cycloheteroalkyl" refers to a cycloheteroalkyl group as herein defined which contains one or more substituents, such as halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, heteroaryl, substituted heteroaryl, nitro, cyano, alkylthio, thiol, sulfamido and the like.

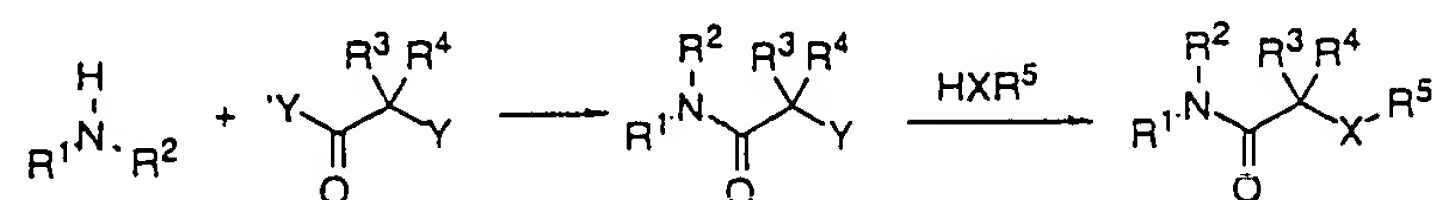
10 The term "alkyl cycloalkyl" refers to the group -R-cycloalkyl where cycloalkyl is a cycloalkyl group and R is a lower alkyl or substituted lower alkyl. Cycloalkyl groups can optionally be unsubstituted or substituted with e.g. halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, heteroaryl, substituted heteroaryl, nitro, cyano, alkylthio, thiol, sulfamido and
15 the like.

If the compound useful in the method of this invention contains a basic group, an acid addition salt may be prepared. Acid addition salts of the compounds are prepared in a standard manner in a suitable solvent from the parent compound and an excess of acid, such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, maleic, succinic, or
20 methanesulfonic. If the final compound contains an acidic group, cationic salts may be prepared. Typically the parent compound is treated with an excess of an alkaline reagent, such as hydroxide, carbonate or alkoxide, containing the appropriate cation. Cations such as Na^+ , K^+ , Ca^{2+} and NH_4^+ are examples of cations present in pharmaceutically acceptable salts.

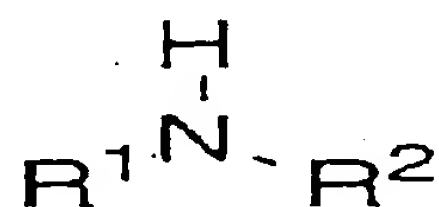
It is within the knowledge of one skilled in the art that stereoisomers of the

compositions described herein as well as isomers and stereoisomers of components that comprise the compositions identified herein all fall within the scope of compositions that are both novel and useful in the therapeutic method of this invention.

The process for manufacturing compounds according to the invention can be
 5 illustrated by way of example by the following reaction scheme:



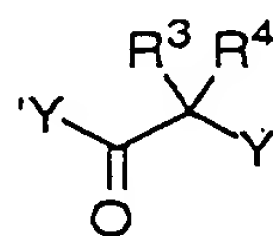
Generally, processes for the synthesis of useful compounds of this invention are characterized by the reaction of compounds of the general formula (1):



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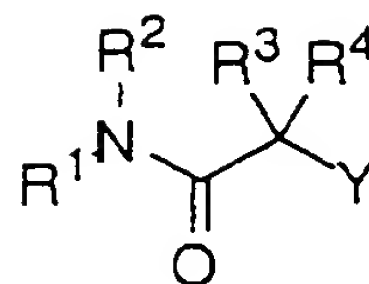
(1)

wherein R^1 and R^2 are substituents as described above. Compound (1) is reacted with a compound (2) of the general formula:



(2)

15 in which R^3 and R^4 have the meaning given above, wherein 'Y is a halide, hydroxyl, or O-acyl and wherein Y represents a halide, and preferably bromine. The reaction of Compound (1) and Compound (2) occurs in inert solvents and in the presence of base and/or auxiliaries, to give compound (3) having the general formula:



(3)

in which R¹, R², R³, R⁴ and Y have the meaning given above. Compound (3) is then reacted with thiols or alcohols of the general formula HXR⁵ in which R⁵ and X each have the meanings given above. Compound (3) is reacted with HXR⁵ in one or more inert solvents, if appropriate, in the presence of base and/or auxiliaries.

Solvents useful in the processes are customary organic solvents that do not change under the reaction conditions. These preferably include ethers such as diethyl ether, dioxane, tetrahydrofuran, glycol dimethyl ether, or alcohols, for example methanol, ethanol, propanol, isopropanol, butanol, iso butanol or tert butanol, or hydrocarbons such as benzene, toluene, xylene, hexane, cyclohexane or petroleum fractions, or halogenated hydrocarbons such as dichloromethane, trichloromethane, tetrachloromethane, dichloroethylene, trichloroethylene or chlorobenzene, or ethyl acetate, triethylamine, pyridine, dimethylsulphoxide, dimethylformamide, hexamethylphosphoramide, acetonitrile, acetone or nitromethane. It is also possible to use mixtures of the solvents mentioned. Dimethylformamide and dimethylsulphoxide are preferred.

Bases which can be employed for the process are in general inorganic or organic bases. These preferably include alkali metal hydroxides, for example sodium hydroxide or potassium hydroxide, alkaline earth metal hydroxides, for example barium hydroxide, alkali metal carbonates such as sodium carbonate or potassium carbonate, alkaline earth metal carbonates such as calcium carbonate, or alkali metal or alkaline earth metal alkoxides such

as sodium or potassium methoxide, sodium or potassium ethoxide or potassium tert-butoxide, or organic amines (trialkyl(C1-C6)-amines) such as triethylamine, or heterocycles such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine, 4-dimethylaminopyridine, methylpiperidine or morpholine. It is also possible to employ as bases alkali metals such as sodium or their hydrides such as sodium
5 hydride. Potassium carbonate is preferred.

The above mentioned bases can, if appropriate, also be employed as acid-binding auxiliaries. Suitable auxiliaries are also dehydrating reagents. These include, for example, carbodiimides such as diisopropylcarbodiimide, dicyclohexylcarbodiimide or N-(3-
10 dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride or carbonyl compounds such as carbonyldiimidazole or 1,2-oxazolium substituents such as 2-ethyl-5-phenyl-19-oxazolium-3-sulphonate or propanephosphonic anhydride or iso-butyl chloroformate or benzotriazolyloxy-tris-(dimethylamino)phosphonium hexafluorophosphate or diphenyl phosphoramidate or methane-sulphonyl chloride, if appropriate in the presence of bases
15 such as triethylamine or N-ethylmorpholine or N-methylpiperidine or dicyclohexylcarbodiimide and N-hydroxysuccinimide. The acid-binding agents and dehydrating reagents are in general employed in an amount from 0.5 to 3 mol, preferably from 1 to 1.5 mol, relative to 1 mol of the corresponding carboxylic acids.

In general, the base is employed in an amount from 0.05 to 10 mol, preferably from
20 1 to 2 mol, relative to 1 mol of the compound (2).

The processes for manufacturing compounds according to the invention are in general carried out in a temperature of from about -30°C to about 110°C, preferably from about -10°C to about 50°C. The manufacturing processes are in general carried out at normal pressure. However, it is also possible to carry out the processes at elevated pressure

or at reduced pressure (e.g. in a range from 0.5 to 5 bar).

Suitable solvents for the reaction with thiols or alcohols in this case are inert organic solvents which do not change under the reaction conditions. These preferably include ethers, such as diethyl ether or tetrahydrofuran, halogenated hydrocarbons such as
5 dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane, trichloroethane, tetrachloroethane, 1,2-dichloroethylene or trichloroethylene, hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane or petroleum fractions, nitromethane, dimethylformamide, acetone, acetonitrile or hexamethylphosphoramide. It is also possible to employ mixtures of the solvents. Dichloromethane, tetrahydrofuran, dimethylformamide,
10 or dimethylsulfoxide is particularly preferred.

Bases useful in the synthesis process are, in general, inorganic or organic bases including alkali metal hydroxides, for example sodium hydroxide or potassium hydroxide, alkaline earth metal hydroxides, for example barium hydroxide, alkali metal carbonates such as sodium carbonate or potassium carbonate, alkaline earth metal carbonates such as
15 calcium carbonate, or alkali metal or alkaline earth metal alkoxides such as sodium or potassium methoxide, sodium or potassium ethoxide or potassium tert-butoxide, or organic amines (trialkyl(C1-C6)amines) such as triethylamine, or heterocycles such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine, dimethylaminopyridine, methylpiperidine or morpholine. It is also possible to employ alkali
20 metals such as sodium and their hydrides such as sodium hydride as bases. Sodium and potassium carbonate and triethylamine are preferred bases.

The base is employed in an amount from 1 mol to 5 mol, preferably from 1 mol to 3 mol, relative to 1 mol of the appropriate thiol or alcohol.

Processes for preparing useful compositions of this invention are illustrated in Examples 1-3.

The compounds of the present invention are useful for treating mammalian disorders such as eating disorders, obesity, hypertension, depression, brain or bodily disorders, and any other disorders mediated by NPY and the related Y5 receptor. It is preferred that the method of this invention is used to treat obesity and eating disorders such as and bulimia. Specifically, the method of this invention can be used to inhibit the onset of obesity and to mediate the appetite in order to control and to reduce obesity mammals such as humans. It is most preferred that the method of this invention is used to treat obesity in humans.

The compounds of the present invention are useful for treating disorders mediated by NPY via the Y5 receptor in mammals. For purposes of this disclosure, mammals includes humans, livestock, zoo animals, laboratory animals, experimental animals and pets. Livestock and related animals include, mammals such as cattle, horses, sheep, pigs, goats, camels, water buffaloes, donkeys, rabbits, fallow deer, reindeer; fur-bearing animals such as mink, chinchilla and raccoon; birds such as chickens, geese, turkeys and ducks. Laboratory animals and experimental animals include mice, rats, guinea pigs, golden hamsters, and pets include dogs, cats, rats, mice, guinea pigs, pigs, and the like.

The compounds of this invention may be administered to mammals both prophylactically and therapeutically by any administration protocol that is capable of supplying at least one compound of this invention to a Y5 receptor. Non-limiting examples of useful administration protocols include orally, parenterally, dermally, transdermally, rectally, nasally or by any other suitable pharmaceutical composition administration protocol that is within the knowledge of one skilled in the art.

The substituted α -alkoxy and α -thioalkoxyamide compositions of this invention will be administered in suitable pharmaceutical dosage forms. The pharmaceutical dosage form will depend largely upon the administration protocol used. The term pharmaceutical dosage form refers to items such as tablets, capsules, liquids and powders, comprising Y5 receptor
5 inhibitors of this invention alone or in the presence of one or more pharmaceutical additives. The choice of additives e.g., excipients and adjuvants again will depend largely upon the chosen administration protocol.

The speed at which the useful compounds of this invention are taken up by the body may also be controlled by combining the useful compositions of this invention with suitable
10 pharmaceutical additives. For example, useful compounds may be combined with suitable additives to give a sustained or delayed release formulation. Alternatively, the useful compounds of this invention may be combined with additives to give an immediate or fast release dosage form. The substituted α -alkoxy and α -thioalkoxyamide compositions of this invention can also be incorporated into food products such as biscuits and cookies. In essence,
15 the compositions can be used as a dietary supplement to reduce or inhibit appetite. Those skilled in the pharmaceutical arts will recognize a wide variety of formulations and vehicles for administering compositions of this invention.

The administration protocol will largely dictate the final form and composition of pharmaceutical dosage forms comprising the Y5 receptor antagonists of this invention. For
20 example, internal administration of compounds of this invention is effected, orally, in the form of powders, tablets, capsules, pastes, drinks, granules, or solutions, suspensions and emulsions which can be administered orally, or bolus, in medicated food, or in drinking water. Internal administration may also be accomplished using a timed release formulation including additives such as surfactant or starch coated capsules, or using a quick release

formulation such as a freeze-dried fast dissolving tablet. Dermal administration is effected, for example, in the form of transdermal patches, spraying or pouring-on and spotting-on. Parenteral administration is effected, for example, in the form of injection (intramuscularly, subcutaneously, intravenously, intraperitoneally) or by implants.

5 Suitable pharmaceutical dosage forms incorporating the Y5 receptor antagonists of this invention include but are not limited to solutions such as solutions for injection, oral solutions, concentrates for oral administration after dilution, solutions for use on the skin or in body cavities, pour-on and spot-on formulations, gels; emulsions and suspension for oral or dermal administration and for injection; semi-solid preparations; formulations in which
10 the active compound is incorporated in cream base or in an oil-in-water or water-in-oil emulsion base; solid preparations such as powders, premixes or concentrates, granules, pellets, tablets, boli, capsules; aerosols and inhalants, and shaped articles containing active compound.

 Pharmaceutical dosage forms that are solutions may be administered by injection
15 intravenously, intramuscularly and subcutaneously. Solutions for injection are prepared by dissolving the active compound in a suitable solvent and, if appropriate, adding adjuvants such as solubilizers, acids, bases, buffer salts, antioxidants and preservatives. The solutions are sterile-filtered and drawn off.

 Alternatively, solutions including compositions of this invention may be
20 administered orally. Concentrates of compositions of this invention are preferably administered orally only after diluting the concentrate to the administration concentration. Oral solutions and concentrates are prepared as described above in the case of the solutions for injection. Solutions for use on the skin are applied dropwise, brushed on, rubbed in, splashed on or sprayed on. These solutions are prepared as described above in the case of

solutions for injection.

Gels are applied to the skin, or introduced into body cavities. Gels are prepared by treating solutions which have been prepared as described in the case of the solutions for injection with such an amount of thickener that a clear substance of cream-like consistency
5 is formed, or by any other means known to one skilled in the art.

Pour-on and spot-on formulations are poured onto, or splashed onto, limited areas of the skin, the active compound penetrating the skin and acting systemically. Pour-on and spot-on formulations are prepared by dissolving, suspending or emulsifying the active compound in suitable solvents or solvent mixtures which are tolerated by the skin. If
10 appropriate, other adjuvants such as colorants, resorption accelerators, antioxidants, light stabilizers, and tackifiers are added.

Emulsions can be administered orally, dermally or in the form of injections. Emulsions are either of the water-in-oil type or of the oil-in-water type. They are prepared by dissolving Y5 receptor antagonists either in the hydrophobic or in the hydrophilic phase
15 and homogenizing the phase with a solvent of the opposite phase with the aid of suitable adjuvants such as emulsifiers, colorants, resorption accelerators, preservatives, antioxidants, light stabilizers, and viscosity-increasing substances.

Suspensions can be administered orally, dermally or in the form of injection. They are prepared by suspending the active compound in a liquid if appropriate with the addition
20 of further adjuvants such as wetting agents, colorants, resorption accelerators, preservatives, antioxidants and light stabilizers.

The pharmaceutical compositions of this invention may include one or more additives in the form of pharmaceutically acceptable additives. Useful additives include solvents, solubilizers, preservatives, thickeners, wetting agents, colorants, resorption

accelerators, antioxidants, light stabilizers, tackifiers, viscosity increasing substances, fillers, flavorings, lubricating agents, and any other pharmaceutical composition additive known to those skilled in the art.

The additive may be a solvent such as water, alcohols such as ethanol, butanol, benzyl alcohol, glycerol, propylene glycol, polyethylene glycols, N-methyl-pyrrolidone, alkanols, glycerol, aromatic alcohols such as benzyl alcohol, phenylethanol, phenoxyethanol, esters such as ethyl acetate, butyl acetate, benzyl benzoate, ethers such as alkylene glycol alkyl ethers such as dipropylene glycol mono-methyl ether, diethylene glycol mono-butyl ether, ketones such as acetone, methyl ethyl ketone, aromatic and/or aliphatic hydrocarbons, vegetable or synthetic oils, DMF, dimethylacetamide, N-methyl-pyrrolidone, 2,2-dimethyl-4-oxy-methylene-1,3-dioxolane.

The following additives may be useful as solubilizers of the compositions of this invention: solvents which enhance solution of the active compound in the main solvent or which prevent its precipitation. Examples are polyvinylpyrrolidone, polyoxyethylated castor oil, polyoxyethylated sorbitan esters.

Useful preservatives are, for example, benzyl alcohol, trichlorobutanol, p-hydroxybenzoic esters, and n-butanol.

Useful thickeners include inorganic thickeners such as bentonite, colloidal silica, aluminum monostearate, organic thickeners such as cellulose derivatives, polyvinyl alcohols and their copolymers, acrylates and methacrylates.

Other liquids which may be useful in pharmaceutical dosage forms of this invention are, for example, homogeneous solvents, solvent mixtures, and wetting agents (dispersants) which are typically surfactants.

Useful colorants are all colorants which are non-toxic and which can be dissolved or suspended.

Useful resorption accelerators are DMSO, spreading oils such as isopropyl myristate, dipropylene glycol pelargonate, silicone oils, fatty acid esters, triglycerides, fatty
5 alcohols.

Useful antioxidants are sulphites or metabisulphites such as potassium metabisulphite, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole, tocopherol.

A useful light stabilizer is novantisolic acid.

Useful tackifiers include cellulose derivatives, starch derivatives, polyacrylates,
10 natural polymers such as alginates, gelatin.

Useful emulsifiers include non-ionic surfactants such as polyoxyethylated castor oil, polyoxyethylated sorbitan monooleate, sorbitan monostearate, glycerol monostearate, polyoxyethyl stearate, alkylphenol polyglycol ethers; ampholytic surfactants such as Di-Na N-lauryl- beta -iminodipropionate or lecithin; anionic surfactants, such as Na-lauryl
15 sulphate, fatty alcohol ether sulphates, the monoethanolamine salt of mono/dialkylpolyglycol ether orthophosphoric esters; cationic surfactants such as cetyltrimethylammonium chloride.

Useful viscosity-increasing substances and substances which stabilize a therapeutic emulsion include carboxymethylcellulose, methylcellulose and other cellulose and starch
20 derivatives, polyacrylates, alginates, gelatin, gum Arabic, polyvinylpyrrolidone, polyvinyl alcohol, copolymers of methyl vinyl ether and maleic anhydride, polyethylene glycols, waxes, colloidal silica or mixtures of the substances mentioned.

To prepare solid pharmaceutical dosage forms, the active compound is mixed with suitable additives, if appropriate with the addition of adjuvants, and the mixture is

formulated as desired. Examples of physiologically acceptable solid inert additives include sodium chloride, carbonates such as calcium carbonate, hydrogen carbonates, aluminum oxides, silicas, clays, precipitated or colloidal silicon dioxide, and phosphates. Examples of solid organic additives include sugars, cellulose, foods such as dried milk, animal meals, 5 cereal meals and coarse cereal meals and starches. Other suitable additives include lubricants and gliding agents such as magnesium stearate, stearic acid, talc, bentonites; disintegrants such as starch or crosslinked polyvinylpyrrolidone; binders such as, starch, gelatin or linear polyvinylpyrrolidone; and dry binders such as microcrystalline cellulose.

In the pharmaceutical dosage forms described herein, the active compounds can be 10 present in the form of a mixture with at least one other Y5 receptor antagonist compound. Alternatively, or in addition, the pharmaceutical dosage forms of the invention can, in addition to at least one Y5 receptor antagonist, include any pharmaceutical compound that is capable of treating any known malady or disorder where the administration of both together create no unacceptable adverse effects.

15 Methods for treating NPY mediated diseases and disorders comprises the administration of an effective quantity of the chosen compound or combinations thereof, preferably dispersed in a pharmaceutical dosage form. Ready-to-use pharmaceutical dosage forms of this invention contain the active compound in concentrations of from 10 ppm to 20 per cent by weight, and preferably of from 0.1 to 10 per cent by weight. Pharmaceutical 20 dosage forms of this invention that are diluted prior to administration, preferably contain the active compound in concentrations of from 0.5 to 90 per cent by weight, and preferably of from 5 to 50 per cent by weight. In general, it has proved advantageous to administer amounts of approximately 0.01mg to approximately 100 mg of active compound per kg of body weight per day to achieve effective results.

The amount and frequency of administration of pharmaceutical dosage forms comprising Y5 receptor antagonists of this invention will be readily determined by one skilled in the art depending upon, among other factors, the route of administration, age and condition of the patient. These dosage units may be administered one to ten times daily for acute or chronic disease. No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The pharmaceutical dosage forms comprising Y5 receptor antagonists of this invention are made following the conventional techniques of pharmacy involving milling, mixing, granulation, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid additive is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

While the compositions described herein may be administered as described above, (*i.e.*, intramuscular, intravenous and subcutaneous etc...), it is preferred that the method of this invention is achieved by administering the compound described herein orally. When the oral administration route is chosen, a larger quantity of reactive agent will be required to produce the same effect as a smaller quantity given for example parenterally. In accordance with good clinical practice, it is preferred to administer the compound according to this method at a concentration level that would produce effective therapeutic results without causing any harmful side effects.

The compositions of this invention have non-therapeutic utility as well. The compositions of this invention are useful as analytical standards for Y5 receptor agonist or antagonist assays.

Compounds 1-136 identified in the Examples and in Tables 1 and 2 below are believed heretofore to be unknown. Known compounds that may be useful in the novel therapeutic method of this invention are disclosed in Table 4 below and are available from Maybridge SPB in Tintagel, Cornwall, Great Britain, from G&J Research Chemicals, Ltd., Great Britain, or are known in the literature.

EXAMPLES

The following specific examples are included as illustrations and are not to be construed as limiting the scope of the inventions disclosed herein in any way.

The compounds useful in the therapeutic method of this invention are prepared by conventional methods of organic chemistry. Unless otherwise noted, reagents and solvents were obtained from commercial suppliers and were used without further purification.

The following solvent systems were used for analytical thin-layer chromatography (TLC): (A) 50:50 hexane-ethyl acetate, (B) 80:20 methanol-water, (C) 40:60 ethyl acetate-dichloromethane, (D) ethyl acetate, (E) 90:10 chloroform-methanol. TLC was performed on Merck Kieselgel 60 F254 silica gel plates (solvent systems A, C, D, and E); or, Baker Reversed Phase Octadecyl (C₁₈) plates (solvent system B). Detection was effected by exposure to UV light (254 nm) or by immersion in basic aqueous potassium permanganate solution. Chromatography was performed using Silica Gel 60 (#9385-5) from EM Science.

Melting points were recorded in open capillary tubes and are uncorrected.

¹H NMR spectra were determined at 300 MHz using a General Electric GE-OMEGA 300 spectrometer. Chemical shifts are reported in parts per million (δ) values relative to tetramethylsilane as internal standard. Spin multiplicities are reported using the

following abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Coupling constants are in Hertz.

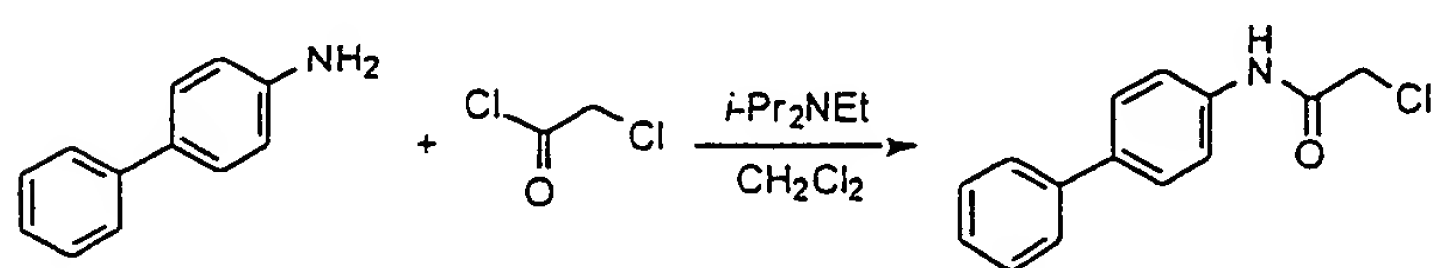
Fast atom bombardment (FAB) mass spectra were recorded using a Kratos Concept 1 spectrometer; electron impact (EI) and chemical ionization (CI) mass spectra were recorded using a Hewlett-Packard MS Engine (HP5989A) spectrometer; liquid chromatography-mass spectra (LC-MS) were recorded using a Finnigan MAT LCQ spectrometer.

Rainin high performance liquid chromatography (HPLC) systems with UV detectors at 254 nm were used under the following conditions: (N) C₁₈ Reversed Phase Cartridge Column (Perkin Elmer/PE Xpress #0258-0164); 20:80 (0.1:99.9 trifluoroacetic acid-acetonitrile)-(0.1:2:97.9 trifluoroacetic acid-acetonitrile-water) to 95:5 (0.1:99.9 trifluoroacetic acid-acetonitrile)-(0.1:2:97.9 trifluoroacetic acid-acetonitrile-water) over 8 minutes, 95:5 (0.1:99.9 trifluoroacetic acid-acetonitrile)-(0.1:2:97.9 trifluoroacetic acid-acetonitrile-water) for 2 minutes; 3 mL/min. (O) Rainin Microsorb 80-225-C5 C₁₈ Reversed Phase column with Microsorb 80-200-G5 C₁₈ Reversed Phase guard column; 50:50 (0.1:99.9 trifluoroacetic acid-acetonitrile)-(0.1:2:97.9 trifluoroacetic acid-acetonitrile-water) to 100:0 (0.1:99.9 trifluoroacetic acid-acetonitrile)-(0.1:2:97.9 trifluoroacetic acid-acetonitrile-water) over 5 minutes, 0.1:99.9 trifluoroacetic acid-acetonitrile for 5 minutes; 1 mL/min.

EXAMPLE 1

Preparation of Intermediate - N-Biphenyl-2-chloroacetamide

Intermediates to the compositions of this invention were prepared according to the method of this Example. Specifically, an N-biphenyl-2-chloroacetamide intermediate was
5 prepared as follows:



4-Aminobiphenyl (1.13 g, 6.70 mmol) was added to a mixture of chloroacetyl chloride (0.532 mL, 6.70 mmol) and diisopropylethylamine (1.16 mL, 6.70 mmol) in dichloromethane (40 mL). After 4 hours the mixture was diluted with ethyl acetate and
10 washed with 1 N hydrochloric acid, water, and saturated aqueous sodium chloride solution, dried (MgSO_4), and concentrated in vacuo to give the desired material as a colorless solid (1.56 g, 95%). ^1H NMR (CDCl_3 , 300 MHz) δ 8.3 (br s, 1 H), 7.57 - 7.66 (m, 6 H), 7.44 - 7.47 (m, 2 H), 7.36 (m, 1 H), 4.23 (s, 2 H).

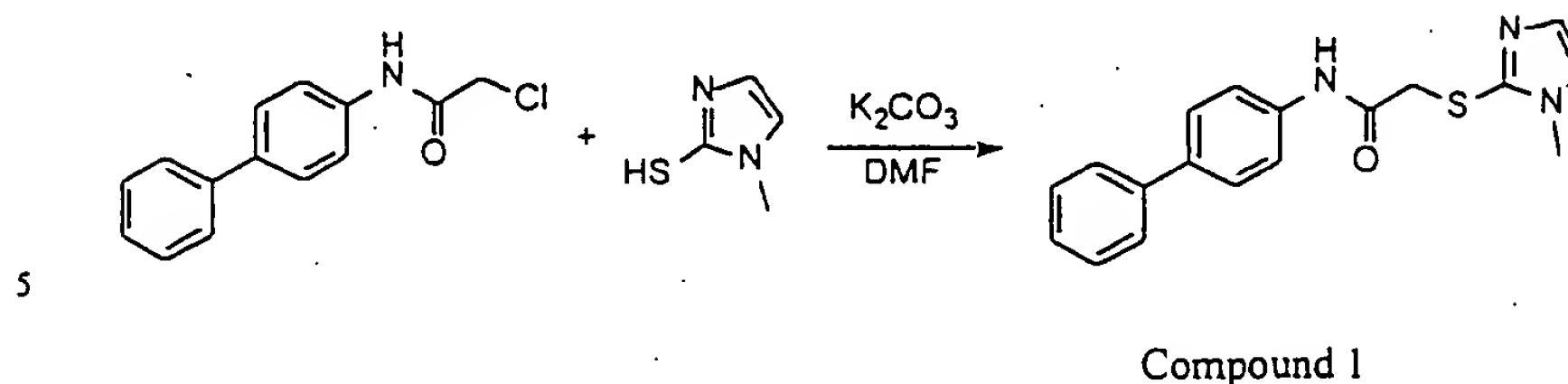
Using the same or analogous methods, intermediates were prepared that were
15 subsequently used according to the methods set forth in the Examples below to synthesize compounds of this invention.

EXAMPLE 2

Preparation of Compound 1

N-Biphenyl-4-yl-2-(1-methyl-1H-imidazol-2-ylsulfanyl)-acetamide

Compound 1 was prepared according to the following general method:



A mixture of 2-mercapto-1-methylimidazole (294 mg, 2.6 mmol), potassium carbonate (391 mg, 2.8 mmol), and N-biphenyl-2-chloroacetamide (630 mg, 2.6 mmol; from Example 1) in N,N-dimethylformamide (12 mL) was stirred overnight. The mixture
10 was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried (MgSO₄), and concentrated in vacuo. The residue was purified by flash column chromatography using a gradient (chloroform, 5% methanol / chloroform, 10% methanol / chloroform) to give the desired material as a colorless solid (560 mg, 67%): mp 151-154°C. ¹H NMR (DMSO-*d*₆, 300
15 MHz) δ 10.44 (s, 1 H), 7.58-7.66 (m, 6 H), 7.41 (m, 2H), 7.23 (s, 1 H), 7.27 (m, 1 H), 6.95 (s, 1 H), 3.52 (s, 2 H), 3.35 (s, 3 H). FAB-MS 324 (M + H⁺).

The compounds in Table 1, below, were prepared by methods analogous to the method used above to prepare Compound 1.

TABLE 1

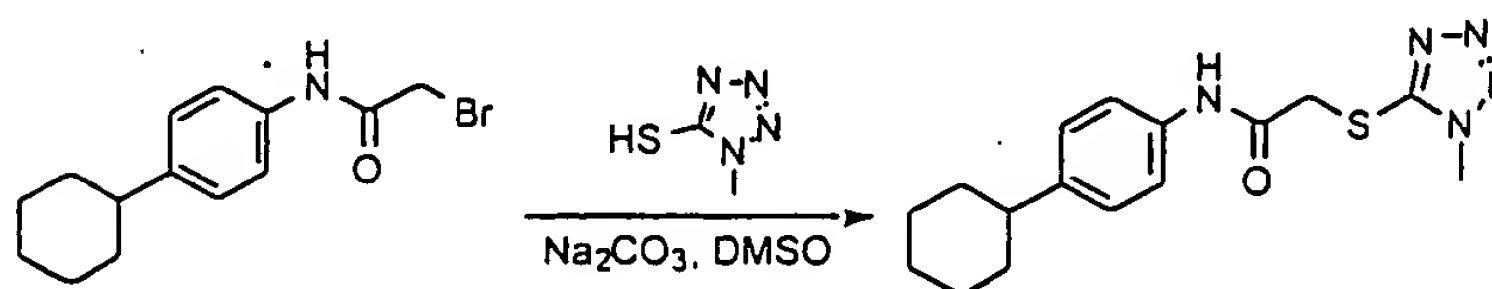
Composition	Name	% Yield	MP (°C)	TLC	MS
2	2-[4-Methyl-5-(5-methyl-isoxazol-3-yl)-4H-[1,2,4]triazol-3-ylsulfanyl]-N-(4-trifluoromethyl-phenyl)-acetamide				
3	N-(4-Cyclohexyl-phenyl)-2-(1-methyl-1H-imidazol-2-ylsulfanyl)-acetamide Hydrochloride		176-177	0.40 (D)	329 (M ⁺ , EI)
4	N-(4-Benzoyl-phenyl)-2-(1H-imidazol-2-ylsulfanyl)-acetamide	79		0.30 (A)	338 (M ⁺ H ⁺ , FAB)
5	N-(4-Cyclohexyl-phenyl)-2-(4-methyl-pyrimidin-2-ylsulfanyl)-acetamide Hydrochloride	52	158	0.61 (A)	342 (M ⁺ H ⁺ , FAB)
6	2-Phenoxy-pentanedioic acid bis-o-tolylamide				
7	2-Phenylsulfanyl-pentanedioic acid bis-phenylamide				

EXAMPLE 3

5 Preparation of Compound 8

N-(4-Cyclohexyl-phenyl)-2-(1-methyl-1H-tetrazol-5-ylsulfanyl)-acetamide

Compound 8 was prepared according to both of the following methods:



Compound 8

Method A

A mixture of N-(4-cyclohexyl-phenyl)-2-bromoacetamide (1.48 g, 5.0 mmol), 5-mercapto-1-methyltetrazole (0.58 g, 5.0 mmol), and sodium carbonate (530 mg, 5.0 mmol) in dimethylsulfoxide (50 mL) was stirred at room temperature for 16 hours. The mixture
5 was diluted with water and extracted with ethyl acetate (3x). The combined organic layer was washed with saturated aqueous sodium chloride solution, dried (MgSO₄), and concentrated to give a solid (3.75 g). The crude was recrystallized from ethyl acetate to give N-(4-cyclohexyl-phenyl)-2-(1-methyl-1H-tetrazol-5-ylsulfanyl)-acetamide as a colorless
solid (1.18 g, 71%): mp 204-205°C; ¹H NMR (300 MHz, CDCl₃) δ 9.26 (br s, 1 H), 7.44
10 (d, 2 H), 7.15 (d, 2 H), 4.05 (s, 3 H), 3.96 (s, 2 H), 2.45 (m, 1 H), 1.75 (m, 5 H), 1.37 (m, 5 H). MS m/z 332 (M+H⁺); Anal Calcd for C₁₆H₂₁N₅OS: C, 57.98; H, 6.39; N, 21.13. Found: C, 58.01; H, 6.34; N, 21.32.

Method B

A mixture of N-(4-cyclohexyl-phenyl)-2-bromoacetamide (29.6 mg, 0.10 mmol), 5-
15 mercapto-1-methyltetrazole (11.6 mg, 0.10 mmol), and potassium carbonate (13.8 mg, 0.1 mmol) in dimethylsulfoxide (1.0 mL) was stirred 1 hour. The mixture was filtered through a short pad of Celite in a pasteur pipette. TLC R_f 0.28 (silica gel, 50:50 hexane / ethyl acetate); HPLC 4.53 min (C18 Cartridge column (Perkin Elmer/PE Xpress #0258-0164) 20:80 Acetonitrile / water to 95:5 acetonitrile / water); LC-MS 332 (M + H⁺). The filtrate
20 was tested directly in the in vitro biological assays.

If desired, the pure compound could be isolated: The filtrate was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution (2x), dried (MgSO₄), and concentrated to give a solid (31 mg).

The crude product was recrystallized from ethyl acetate to give the product as a colorless solid (19 mg, 58%). mp 203-205°C; the ¹H NMR was identical to that of the material prepared by Method A; and, in TLC analysis using 50:50 hexane-ethyl acetate, the product co-eluted with the material prepared using Method A.

5 The compounds listed in Table 2, below, were prepared by methods analogous to the methods used above to prepare compound 8. NR in Table 2 indicates no data was recorded.

TABLE 2

Composition	Name	TLC	HPLC	MS
9	N-(4-Benzoyl-phenyl)-2-(1-methyl-1H-imidazol-2-ylsulfanyl)-acetamide	0.14 (A), 0.50 (B)	2.15 (N)	352 (M+H+, LC-MS)
10	N-(4-Benzoyl-phenyl)-2-(1H-imidazol-2-ylsulfanyl)-acetamide	0.11 (A), 0.56 (B)	1.93 (N)	338 (M+H+, LC-MS)
11	2-(1H-Benzoimidazol-2-ylsulfanyl)-N-(4-cyclohexyl-phenyl)-acetamide	0.52 (A), 0.18 (B)	4.44 (N)	366 (M+H+, LC-MS)
12	2-(1H-Benzoimidazol-2-ylsulfanyl)-N-(4-benzoyl-phenyl)-acetamide	0.34 (A), 0.37 (B)	3.03 (N)	388 (M+H+, LC-MS)
13	2-(2-Amino-6-hydroxy-9H-purin-8-ylsulfanyl)-N-(4-cyclohexyl-phenyl)-acetamide	0.00 (A)	NR	399 (M+H+, LC-MS)
14	2-(2-Amino-6-hydroxy-9H-purin-8-ylsulfanyl)-N-(4-benzoyl-phenyl)-acetamide	0.02 (A)	NR	421 (M+H+, LC-MS)
15	N-(4-Cyclohexyl-phenyl)-2-(4,5-diphenyl-1H-imidazol-2-ylsulfanyl)-acetamide	0.08 (B)	5.77 (N)	
16	N-(4-Benzoyl-phenyl)-2-(4,5-diphenyl-1H-imidazol-2-ylsulfanyl)-acetamide	0.45 (A), 0.22 (B)	4.34 (N)	490 (M+H+, LC-MS)
17	N-(4-Cyclohexyl-phenyl)-2-(5-nitro-1H-benzoimidazol-2-ylsulfanyl)-acetamide	0.32 (A), 0.22 (B)	5.63 (N)	411 (M+H+, LC-MS)
18	N-(4-Benzoyl-phenyl)-2-(5-nitro-1H-benzoimidazol-2-ylsulfanyl)-acetamide	0.10 (A)	4.27 (N)	433 (M+H+, LC-MS)
19	N-(4-Cyclohexyl-phenyl)-2-(5-methoxy-1H-benzoimidazol-2-ylsulfanyl)-acetamide	0.35 (A), 0.19 (B)	4.60 (N)	396 (M+H+, LC-MS)
20	N-(4-Benzoyl-phenyl)-2-(5-methoxy-1H-benzoimidazol-2-ylsulfanyl)-acetamide	0.19 (A), 0.39 (B)	3.20 (N)	418 (M+H+, LC-MS)
21	N-(4-Cyclohexyl-phenyl)-2-(5-methyl-1H-benzoimidazol-2-ylsulfanyl)-acetamide	0.51 (A), 0.14 (B)	NR	380 (M+H+, LC-MS)
22	N-(4-Benzoyl-phenyl)-2-(5-methyl-1H-benzoimidazol-2-ylsulfanyl)-acetamide	0.33 (A), 0.32 (B)	3.36 (N)	402 (M+H+, LC-MS)
23	N-(4-Cyclohexyl-phenyl)-2-{9-[(2R,3R,4R,5R)-3,4-dihydroxy-5-hydroxymethyl-tetrahydrofuran-2-yl]-9H-purin-6-ylsulfanyl}-acetamide	0.00 (A), 0.41 (B)	3.50 (N)	500 (M+H+, LC-MS)

Composition	Name	TLC	HPLC	MS
24	N-(4-Benzoyl-phenyl)-2-{9-[(2R,3R,4R,5R)-3,4-dihydroxy-5-hydroxymethyl-tetrahydro-furan-2-yl]-9H-purin-6-ylsulfanyl}-acetamide	0.00 (A), 0.67 (B)	2.40 (N)	522 (M+H+), LC-MS
25	N-(4-Cyclohexyl-phenyl)-2-(4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetamide	NR	NR	394 (M+H+), LC-MS
28	N-(4-Benzoyl-phenyl)-2-(7H-purin-6-ylsulfanyl)-acetamide	0.05 (A), 0.62 (B)	2.54 (N)	390 (M+H+), LC-MS
29	N-(4-Cyclohexyl-phenyl)-2-(4-methyl-pyrimidin-2-ylsulfanyl)-acetamide	0.42 (A), 0.29 (B)	5.06 (N)	342 (M+H+), LC-MS
30	N-(4-Benzoyl-phenyl)-2-(4-methyl-pyrimidin-2-ylsulfanyl)-acetamide	0.23 (A), 0.54 (B)	3.59 (N)	364 (M+H+), LC-MS
31	N-(4-Cyclohexyl-phenyl)-2-(4,5-dihydro-thiazol-2-ylsulfanyl)-acetamide	0.67 (A), 0.24 (B)	4.64 (N)	335 (M+H+), LC-MS
32	N-(4-Benzoyl-phenyl)-2-(4,5-dihydro-thiazol-2-ylsulfanyl)-acetamide	0.41 (A), 0.46 (B)	3.25 (N)	357 (M+H+), LC-MS
33	N-(4-Cyclohexyl-phenyl)-2-(2-hydroxy-ethylsulfanyl)-acetamide	0.20 (A), 0.45 (B)	3.82 (N)	294 (M+H+), LC-MS
34	N-(4-Cyclohexyl-phenyl)-2-(2,3-dihydroxy-propylsulfanyl)-acetamide	0.08 (A), 0.50 (B)	3.31 (N)	324 (M+H+), LC-MS
35	N-(4-Cyclohexyl-phenyl)-2-(1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl)-acetamide	0.22 (A)	4.41 (N)	368 (M+H+), LC-MS
36	N-(4-Cyclohexyl-phenyl)-2-(1-oxy-pyridin-2-ylsulfanyl)-acetamide	0.09 (A), 0.41 (B)	3.60 (N)	343 (M+H+), LC-MS
37	2-(Benzothiazol-2-ylsulfanyl)-N-(4-cyclohexyl-phenyl)-acetamide	0.78 (A)	6.68 (N)	383 (M+H+), LC-MS
38	2-(Benzooxazol-2-ylsulfanyl)-N-(4-cyclohexyl-phenyl)-acetamide	0.75 (A), 0.21 (B)	6.27 (N)	367 (M+H+), LC-MS
39	N-(4-Cyclohexyl-phenyl)-2-(pyrimidin-2-ylsulfanyl)-acetamide	0.34 (A), 0.36 (B)	4.72 (N)	328 (M+H+), LC-MS
40	N-(4-Benzoyl-phenyl)-2-(2-hydroxy-ethylsulfanyl)-acetamide	0.08 (A), 0.65 (B)	2.40 (N)	316 (M+H+), LC-MS
41	N-(4-Benzoyl-phenyl)-2-(pyridin-4-ylsulfanyl)-acetamide	0.11 (A), 0.49 (B)	2.18 (N)	349 (M+H+), LC-MS
42	N-(4-Benzoyl-phenyl)-2-(2,3-dihydroxy-propylsulfanyl)-acetamide	0.05 (A), 0.69 (B)	1.97 (N)	346 (M+H+), LC-MS
43	N-(4-Benzoyl-phenyl)-2-(1H-pyrazolo[3,4-d]pyrimidin-4-ylsulfanyl)-acetamide	0.08 (A), 0.54 (B)	3.10 (N)	390 (M+H+), LC-MS
44	N-(4-Benzoyl-phenyl)-2-(pyridin-2-ylsulfanyl)-acetamide	0.52 (A), 0.45 (B)	3.77 (N)	349 (M+H+), LC-MS
45	N-(4-Benzoyl-phenyl)-2-(1-methyl-1H-tetrazol-5-ylsulfanyl)-acetamide	0.12 (A)	3.09 (N)	354 (M+H+), LC-MS
46	N-(4-Benzoyl-phenyl)-2-(1-oxy-pyridin-2-ylsulfanyl)-acetamide	0.05 (A), 0.65 (B)	2.26 (N)	365 (M+H+), LC-MS
47	2-(Benzothiazol-2-ylsulfanyl)-N-(4-benzoyl-phenyl)-acetamide	0.66 (A), 0.28 (B)	5.21 (N)	405 (M+H+), LC-MS
48	2-(Benzooxazol-2-ylsulfanyl)-N-(4-benzoyl-phenyl)-acetamide	0.60 (A), 0.35 (B)	4.84 (N)	389 (M+H+), LC-MS

Composition	Name	TLC	HPLC	MS
49	N-(4-Benzoyl-phenyl)-2-(pyrimidin-2-ylsulfanyl)-acetamide	0.20 (A), 0.60 (B)	3.26 (N)	350 (M+H+, LC-MS)
50	N-(4-Cyclohexyl-phenyl)-2-(pyridin-4-ylsulfanyl)-acetamide	0.12 (A), 0.27 (B)	3.54 (N)	327 (M+H+, LC-MS)
51	2-(5-Amino-[1,3,4]thiadiazol-2-ylsulfanyl)-N-(4-cyclohexyl-phenyl)-acetamide	0.05 (A), 0.44 (B)	3.68 (N)	349 (M+H+, LC-MS)
52	N-(4-Cyclohexyl-phenyl)-2-(1-phenyl-1H-tetrazol-5-ylsulfanyl)-acetamide	0.68 (A), 0.23 (B)	5.90 (N)	394 (M+H+, LC-MS)
53	N-(4-Cyclohexyl-phenyl)-2-(4-fluoro-phenylsulfanyl)-acetamide	0.80 (A)	6.05 (N)	344 (M+H+, LC-MS)
54	2-(4-Acetylamino-phenylsulfanyl)-N-(4-cyclohexyl-phenyl)-acetamide	0.11 (A)	4.60 (N)	383 (M+H+, LC-MS)
55	N-(4-Cyclohexyl-phenyl)-2-(4-hydroxy-phenylsulfanyl)-acetamide	0.51 (A), 0.38 (B)	4.84 (N)	342 (M+H+, LC-MS)
56	N-(4-Cyclohexyl-phenyl)-2-(1H-[1,2,4]triazol-3-ylsulfanyl)-acetamide	0.14 (A), 0.47 (B)	3.64 (N)	317 (M+H+, LC-MS)
57	2-(5-Amino-2H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-cyclohexyl-phenyl)-acetamide	0.06 (A), 0.48 (B)	3.27 (N)	332 (M+H+, LC-MS)
58	2-(2-Amino-7H-purin-6-ylsulfanyl)-N-(4-cyclohexyl-phenyl)-acetamide	0.06 (A), 0.39 (B)	3.25 (N)	383 (M+H+, LC-MS)
59	2-(4-Amino-1H-pyrazolo[3,4-d]pyrimidin-6-ylsulfanyl)-N-(4-cyclohexyl-phenyl)-acetamide	0.05 (A)	3.41 (N)	383 (M+H+, LC-MS)
60	N-(4-Benzoyl-phenyl)-2-(6-ethoxy-benzothiazol-2-ylsulfanyl)-acetamide	0.63 (A), 0.18 (B)	5.85 (N)	449 (M+H+, LC-MS)
61	2-(5-Amino-[1,3,4]thiadiazol-2-ylsulfanyl)-N-(4-benzoyl-phenyl)-acetamide	0.03 (A), 0.66 (B)	2.44 (N)	371 (M+H+, LC-MS)
62	N-(4-Benzoyl-phenyl)-2-(1-phenyl-1H-tetrazol-5-ylsulfanyl)-acetamide	0.41 (A)	4.63 (N)	416 (M+H+, LC-MS)
63	N-(4-Benzoyl-phenyl)-2-(4-fluoro-phenylsulfanyl)-acetamide	0.64 (A), 0.42 (B)	4.78 (N)	366 (M+H+, LC-MS)
64	2-(4-Acetylamino-phenylsulfanyl)-N-(4-benzoyl-phenyl)-acetamide	0.06 (A), 0.57 (B)	3.45 (N)	405 (M+H+, LC-MS)
65	N-(4-Benzoyl-phenyl)-2-(4-hydroxy-phenylsulfanyl)-acetamide	0.09 (A), 0.62 (B)	3.66 (N)	364 (M+H+, LC-MS)
66	N-(4-Benzoyl-phenyl)-2-(1H-[1,2,4]triazol-3-ylsulfanyl)-acetamide	0.05 (A), 0.71 (B)	2.39 (N)	339 (M+H+, LC-MS)
67	2-(5-Amino-2H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-benzoyl-phenyl)-acetamide	0.02 (A), 0.71 (B)	2.06 (N)	354 (M+H+, LC-MS)
68	2-(2-Amino-7H-purin-6-ylsulfanyl)-N-(4-benzoyl-phenyl)-acetamide	0.02 (A), 0.65 (B)	2.13 (N)	405 (M+H+, LC-MS)
69	2-(4-Amino-1H-pyrazolo[3,4-d]pyrimidin-6-ylsulfanyl)-N-(4-benzoyl-phenyl)-acetamide	0.02 (A)	2.30 (N)	405 (M+H+, LC-MS)
70	2-(4-Amino-6-hydroxy-5-nitroso-pyrimidin-2-ylsulfanyl)-N-(4-benzoyl-phenyl)-acetamide	0.02 (A), 0.89 (B)	NR	410 (M+H+, LC-MS)
71	N-(4-Benzoyl-phenyl)-2-(5-chloro-benzothiazol-2-ylsulfanyl)-acetamide	0.64 (A), 0.22 (B)	5.90 (N)	439, 441 (M+H+, LC- MS)

Composition	Name	TLC	HPLC	MS
72	N-(4-Benzoyl-phenyl)-2-(4,6-dimethyl-pyrimidin-2-ylsulfanyl)-acetamide	0.27 (A), 0.51 (B)	3.91 (N)	378 (M+H+, LC-MS)
73	N-(4-Cyclohexyl-phenyl)-2-(5-methyl-1H-[1,2,4]triazol-3-ylsulfanyl)-acetamide	0.12 (A), 0.38 (B)	3.65 (N)	331 (M+H+, LC-MS)
74	N-(4-Cyclohexyl-phenyl)-2-(quinazolin-4-ylsulfanyl)-acetamide	0.43 (A), 0.13 (B)	6.44 (N)	378 (M+H+, LC-MS)
75	N-(4-Cyclohexyl-phenyl)-2-(4-trifluoromethyl-pyrimidin-2-ylsulfanyl)-acetamide	0.66 (A), 0.23 (B)	7.65 (N)	396 (M+H+, LC-MS)
76	N-(4-Cyclohexyl-phenyl)-2-(4,6-diamino-pyrimidin-2-ylsulfanyl)-acetamide	0.06 (A), 0.43 (B)	4.50 (N)	358 (M+H+, LC-MS)
77	N-(4-Cyclohexyl-phenyl)-2-(6-ethoxy-benzothiazol-2-ylsulfanyl)-acetamide	0.78 (A)	9.46 (N)	427 (M+H+, LC-MS)
78	2-(4-Amino-6-hydroxy-5-nitroso-pyrimidin-2-ylsulfanyl)-N-(4-cyclohexyl-phenyl)-acetamide	0.03 (A)	4.53 (N)	388 (M+H+, LC-MS)
79	2-(5-Chloro-benzothiazol-2-ylsulfanyl)-N-(4-cyclohexyl-phenyl)-acetamide	0.75 (A)	9.65 (N)	417, 419 (M+H+, LC- MS)
80	N-(4-Cyclohexyl-phenyl)-2-(4,6-dimethyl-pyrimidin-2-ylsulfanyl)-acetamide	0.43 (A), 0.25 (B)	6.98 (N)	356 (M+H+, LC-MS)
81	N-(4-Benzoyl-phenyl)-2-(5-methyl-1H-[1,2,4]triazol-3-ylsulfanyl)-acetamide	0.06 (A), 0.63 (B)	3.26 (N)	353 (M+H+, LC-MS)
82	N-(4-Benzoyl-phenyl)-2-(quinazolin-4-ylsulfanyl)-acetamide	0.25 (A), 0.35 (B)	5.11 (N)	400 (M+H+, LC-MS)
83	N-(4-Benzoyl-phenyl)-2-(4-trifluoromethyl-pyrimidin-2-ylsulfanyl)-acetamide	0.51 (A), 0.48 (B)	5.76 (N)	418 (M+H+, LC-MS)
84	N-(4-Benzoyl-phenyl)-2-(4,6-diamino-pyrimidin-2-ylsulfanyl)-acetamide	0.02 (A), 0.66 (B)	3.00 (N)	380 (M+H+, LC-MS)
85	N-(4-Benzoyl-phenyl)-2-(3-phenyl-[1,2,4]oxadiazol-5-ylsulfanyl)-acetamide	0.58 (A)	6.83 (N)	416 (M+H+, LC-MS)
86	N-(4-Benzoyl-phenyl)-2-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanyl)-acetamide	0.17 (A), 0.54 (B)	4.38 (N)	370 (M+H+, LC-MS)
87	N-(4-Benzoyl-phenyl)-2-[1-(4-hydroxy-phenyl)-1H-tetrazol-5-ylsulfanyl]-acetamide	0.06 (A), 0.58 (B)	4.97 (N)	432 (M+H+, LC-MS)
88	N-(4-Benzoyl-phenyl)-2-(7-trifluoromethyl-quinolin-4-ylsulfanyl)-acetamide	0.18 (A)	5.43 (N)	467 (M+H+, LC-MS)
89	N-(4-Benzoyl-phenyl)-2-(5-phenyl-[1,3,4]oxadiazol-2-ylsulfanyl)-acetamide	0.35 (B)	6.01 (N)	416 (M+H+, LC-MS)
90	N-(4-Cyclohexyl-phenyl)-2-(3-phenyl-[1,2,4]oxadiazol-5-ylsulfanyl)-acetamide	0.85 (A)	7.47 (N)	394 (M+H+, LC-MS)
91	N-(4-Cyclohexyl-phenyl)-2-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanyl)-acetamide	0.31 (A), 0.25 (B)	5.32 (N)	348 (M+H+, LC-MS)
92	N-(4-Cyclohexyl-phenyl)-2-[1-(4-hydroxy-phenyl)-1H-tetrazol-5-ylsulfanyl]-acetamide	0.42 (A), 0.30 (B)	5.65 (N)	410 (M+H+, LC-MS)
93	N-(4-Cyclohexyl-phenyl)-2-(7-trifluoromethyl-quinolin-4-ylsulfanyl)-acetamide	0.35 (A), 0.01 (B)	6.05 (N)	445 (M+H+, LC-MS)

Composition	Name	TLC	HPLC	MS
94	N-(4-Cyclohexyl-phenyl)-2-(5-phenyl-[1,3,4]oxadiazol-2-ylsulfanyl)-acetamide	0.65 (A), 0.01 (B)	6.64 (N)	394 (M+H+, LC-MS)
95	N-(4-Cyclohexyl-phenyl)-2-(quinolin-2-ylsulfanyl)-acetamide	0.83 (A), 0.07 (B)	7.50 (N)	377 (M+H+, LC-MS)
96	N-(4-Cyclohexyl-phenyl)-2-(3-mercaptomethyl-benzylsulfanyl)-acetamide	0.89 (A), 0.01 (B)	9.62 (N)	368 (LC-MS)
97	2-(2-Amino-phenylsulfanyl)-N-(4-cyclohexyl-phenyl)-acetamide	0.63 (A), 0.27 (B)	5.11 (N)	341 (M+H+, LC-MS)
98	2-(3-Amino-phenylsulfanyl)-N-(4-cyclohexyl-phenyl)-acetamide	0.54 (A), 0.33 (B)	4.18 (N)	341 (M+H+, LC-MS)
99	2-(4-Amino-phenylsulfanyl)-N-(4-cyclohexyl-phenyl)-acetamide	0.48 (A), 0.39 (B)	4.07 (N)	341 (M+H+, LC-MS)
100	N-(4-Benzoyl-phenyl)-2-(quinolin-2-ylsulfanyl)-acetamide	0.62 (A), 0.21 (B)	5.59 (N)	399 (M+H+, LC-MS)
101	N-(4-Benzoyl-phenyl)-2-(3-mercaptomethyl-benzylsulfanyl)-acetamide	0.09 (A), 0.15 (B)	6.25 (N)	
102	2-(3-Amino-phenylsulfanyl)-N-(4-benzoyl-phenyl)-acetamide	0.09 (A), 0.56 (B)	2.70 (N)	363 (M+H+, LC-MS)
103	2-(4-Amino-phenylsulfanyl)-N-(4-benzoyl-phenyl)-acetamide	0.09 (A), 0.59 (B)	2.65 (N)	363 (M+H+, LC-MS)
104	N-(4-Benzoyl-phenyl)-2-(4-mercapto-5-methyl-pyrimidin-2-ylsulfanyl)-acetamide	0.09 (A)	5.69 (N)	396 (M+H+, LC-MS)
105	2-(4-Amino-6-mercapto-[1,3,5]triazin-2-ylsulfanyl)-N-(4-benzoyl-phenyl)-acetamide	0.03 (A), 0.06 (B)	4.95 (N)	398 (M+H+, LC-MS)
106	N-(4-Benzoyl-phenyl)-2-(3-methoxy-phenylsulfanyl)-acetamide	0.55 (A), 0.36 (B)	4.97 (N)	378 (M+H+, LC-MS)
107	N-(4-Benzoyl-phenyl)-2-(2,4,6-trimethyl-benzylsulfanyl)-acetamide	0.68 (A), 0.20 (B)	6.35 (N)	404 (M+H+, LC-MS)
108	N-(4-Benzoyl-phenyl)-2-(4-methylsulfanyl-phenylsulfanyl)-acetamide	0.55 (A), 0.38 (B)	5.38 (N)	394 (M+H+, LC-MS)
109	N-(4-Benzoyl-phenyl)-2-cyclopentylsulfanyl-acetamide	0.69 (A), 0.33 (B)	5.21 (N)	340 (M+H+, LC-MS)
110	N-(4-Benzoyl-phenyl)-2-(furan-2-ylmethylsulfanyl)-acetamide	0.58 (A), 0.47 (B)	4.61 (N)	352 (M+H+, LC-MS)
111	N-(4-Cyclohexyl-phenyl)-2-(5-furan-2-yl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetamide	0.33 (A), 0.34 (B)	4.70 (N)	381 (M+H+, LC-MS)
112	N-(4-Cyclohexyl-phenyl)-2-[4-methyl-5-(3-methylsulfanyl-6,7-dihydro-benzo[C]thiophen-1-yl)-4H-[1,2,4]triazol-3-ylsulfanyl]-acetamide	0.19 (A), 0.06 (B)	6.56 (N)	511 (M+H+, LC-MS)
113	N-(4-Cyclohexyl-phenyl)-2-[5-(4-methoxy-phenyl)-4-(3-trifluoromethyl-phenyl)-4H-[1,2,4]triazol-3-ylsulfanyl]-acetamide	0.15 (A), 0.11 (B)	6.50 (N)	567 (M+H+, LC-MS)
114	N-(4-Cyclohexyl-phenyl)-2-(5-hydroxymethyl-1-methyl-1H-imidazol-2-ylsulfanyl)-acetamide	0.17 (A), 0.34 (B)	3.36 (N)	360 (M+H+, LC-MS)

Composition	Name	TLC	HPLC	MS
115	2-[(4-Cyclohexyl-phenylcarbamoyl)-methylsulfanyl]-3-methyl-3H-imidazole-4-carboxylic acid methyl ester	0.50 (A), 0.19 (B)	4.89 (N)	388 (M+H+, LC-MS)
116	2-(5-Cyclohexylamino-[1,3,4]thiadiazol-2-ylsulfanyl)-N-(4-cyclohexyl-phenyl)-acetamide	0.29 (A), 0.23 (B)	5.60 (N)	431 (M+H+, LC-MS)
117	N-(4-Cyclohexyl-phenyl)-2-[5-[2-(2,4-dichlorophenoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-ylsulfanyl]-acetamide	0.56 (A), 0.06 (B)	6.25 (N)	552 (M+, LC- MS)
118	N-(4-Benzoyl-phenyl)-2-(5-furan-2-yl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetamide	0.13 (A), 0.56 (B)	3.38 (N)	405 (M+H+, LC-MS)
119	N-(4-Benzoyl-phenyl)-2-[4-methyl-5-(3-methylsulfanyl-6,7-dihydro-benzo[C]thiophen-1-yl)-4H-[1,2,4]triazol-3-ylsulfanyl]-acetamide	0.14 (A), 0.10 (B)	5.26 (N)	533 (M+H+, LC-MS)
120	N-(4-Benzoyl-phenyl)-2-[5-(4-methoxy-phenyl)-4-(3-trifluoromethyl-phenyl)-4H-[1,2,4]triazol-3-ylsulfanyl]-acetamide	0.08 (A), 0.23 (B)	5.28 (N)	589 (M+H+, LC-MS)
121	N-(4-Benzoyl-phenyl)-2-(5-hydroxymethyl-1-methyl-1H-imidazol-2-ylsulfanyl)-acetamide	0.06 (A), 0.58 (B)	1.99 (N)	382 (M+H+, LC-MS)
122	2-[(4-Benzoyl-phenylcarbamoyl)-methylsulfanyl]-3-methyl-3H-imidazole-4-carboxylic acid methyl ester	0.31 (A), 0.33 (B)	3.52 (N)	410 (M+H+, LC-MS)
123	N-(4-Benzoyl-phenyl)-2-(5-cyclohexylamino-[1,3,4]thiadiazol-2-ylsulfanyl)-acetamide	0.23 (A), 0.26 (B)	4.29 (N)	453 (M+H+, LC-MS)
124	N-(4-Benzoyl-phenyl)-2-[5-[2-(2,4-dichlorophenoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-ylsulfanyl]-acetamide	0.31 (A), 0.10 (B)	5.96 (N)	574 (M+, LC- MS)
125	N-(4-tert-Butyl-phenyl)-2-(1-methyl-1H-tetrazol-5-ylsulfanyl)-propionamide	0.63 (A), 0.45 (B)	4.22 (N)	320 (M+H+, LC-MS)
126	2-(1-Methyl-1H-tetrazol-5-ylsulfanyl)-N-(2-thiophen-2-yl-ethyl)-acetamide	0.15 (A), 0.75 (B)	1.24 (N)	284 (M+H+, LC-MS)
127	N-(4-Cyclohexyl-phenyl)-2-(1-methyl-1H-tetrazol-5-ylsulfanyl)-propionamide	0.62 (A), 0.32 (B)	5.06 (N)	346 (M+H+, LC-MS)
128	N-Benzothiazol-2-yl-2-(1-methyl-1H-tetrazol-5-ylsulfanyl)-acetamide	0.21 (A), 0.69 (B)	2.33 (N)	307 (M+H+, LC-MS)
129	1-Azepan-1-yl-2-(1-methyl-1H-tetrazol-5-ylsulfanyl)-ethanone	0.22 (A), 0.72 (B)	1.41 (N)	256 (M+H+, LC-MS)
130	N-(9H-Fluoren-2-yl)-2-(1-methyl-1H-tetrazol-5-ylsulfanyl)-acetamide	0.22 (A), 0.53 (B)	3.75 (N)	338 (M+H+, LC-MS)
131	N-(9H-Fluoren-1-yl)-2-(1-methyl-1H-tetrazol-5-ylsulfanyl)-acetamide	0.27 (A), 0.52 (B)	3.70 (N)	338 (M+H+, LC-MS)
132	N-(4-Cyclohexyl-phenyl)-2-phenoxy-acetamide	0.19 (A), 0.86 (B)	6.12 (N)	310 (M+H+, LC-MS)
133	N-(4-Benzoyl-phenyl)-2-(1-methyl-piperidin-4-yloxy)-acetamide	0.10 (A), 0.22 (B)	1.97 (N)	353 (M+H+, LC-MS)

Composition	Name	TLC	HPLC	MS
134	N-(4-Benzoyl-phenyl)-2-phenoxy-acetamide	0.43 (A), 0.76 (B)	4.68 (N)	332 (M+H+, LC-MS)
135	N-(4-Cyclohexyl-phenyl)-2-(1-methyl-piperidin-4-yloxy)-acetamide	0.07 (A), 0.22 (B)	3.35 (N)	331 (M+H+, LC-MS)
136	N-(4-Cyclohexyl-phenyl)-2-(1H-imidazol-2-ylsulfanyl)-acetamide	0.15 (A), 0.36 (B)	3.39 (N)	316 (M+H+, LC-MS)

EXAMPLE 4

The compounds prepared in Examples 2-3 as well as the prior art compounds set forth in Table 4, below, were tested for NPY Y5 receptor binding affinity according to one or more of the protocols set forth below. The test results are reported in Table 3, below.

A. Human NPY1 Receptor Binding Assay

This is a modification of Gordon et al., (J. Neurochem. 55:506-513, 1990). SK-N-MC cells (ATCC, Rockville, MD) were plated in 24-well plates. Once confluent, cells are rinsed with Dulbecco's phosphate buffered saline (DPBS). Cells were then preincubated in binding buffer containing serum-free DMEM, 25 mM HEPES (pH 7.3), 0.5% bovine serum albumin (BSA), 0.1% bacitracin and 0.1 mM phenylmethylsulfonylfluoride for 30 minutes at room temperature. Drug dilution and [125I]PYY (~50 pM: NEN-DuPont) are added to the wells, and the cells are incubated for an additional 3 hours at room temperature, followed by rinsing with ice-cold DPBS. Nonspecific binding is defined with 1 μ M NPY. After lysing the cells with 1% Triton X-100, the amount of radioactivity in the lysates is quantitated with a gamma counter. IC50 values, which correspond to 50% inhibition of specific binding, are determined with non-linear regression analysis. The results of compounds tested according to this protocol are reported in Table 3.

B. Human NPY2 and NPY4/PP1 Receptor Binding Assays

Binding assays were performed on GF/C Millipore 96-well plates pretreated with 0.02% polyethylenimine. The binding buffer for rat Y2 binding is Krebs-Ringer

bicarbonate (pH 7.4) containing 0.01% BSA and 0.005% bacitracin. Samples consist of membrane protein, 25 pM [¹²⁵I]PYY and drug dilution. Nonspecific binding is defined by 1 μM NPY. The binding buffer for human Y4/PP1 binding consists of 137 mM NaCl, 5.4 mM KCl, 0.44 mM KH₂PO₄, 1.26 mM CaCl₂, 0.81 mM MgSO₄, 20 mM HEPES, 1 mM dithiothreitol, 0.1% bacitracin, 100 mg/l streptomycin sulfate, 1 mg/l aprotinin, 10 mg/ml soybean trypsin inhibitor and 0.3% BSA, pH 7.4. Samples consist of membrane protein, 50 pM human [¹²⁵I]human PP (hPP: NEN DuPont, Boston, MA) and drug dilution. 1 μM hPP is used to define nonspecific binding.

After a 2 hour incubation at room temperature with constant mixing, the samples are aspirated on a vacuum manifold, and rinsed with ice-cold binding buffer. The amount of radioactivity in each well is quantitated with either gamma counting or liquid scintillation. IC₅₀ values, which correspond to 50% inhibition of specific binding, are determined with non-linear regression analysis. The results of compounds tested according to this protocol are reported in Table 3.

15 C. Human and Rat NPY5 Receptor Binding Assays

Binding assays are performed on GF/C Millipore 96-well plates pretreated with 0.02% polyethylenimine. The binding buffer is 25 mM Tris, 120 mM NaCl, 5 mM KCl, 1.2 mM KH₂PO₄, 2.5 mM CaCl₂, 1.2 mM MgSO₄, 0.1% BSA and 0.5 mg/ml bacitracin, pH 7.4. Samples consist of membrane protein, 75-100 pM [¹²⁵I]PYY (porcine, NEN-DuPont) and drug dilution. Nonspecific binding is defined by 1 μM PYY. After a 2 hour incubation at room temperature with constant mixing, the samples are aspirated on a vacuum manifold, and rinsed with ice-cold binding buffer. The amount of radioactivity in each well is quantitated with either gamma counting or liquid scintillation. IC₅₀ values, which

correspond to 50% inhibition of specific binding, are determined with non-linear regression analysis. The results of compounds tested according to this protocol are reported in Table 3.

D. Rat NPY5 Cyclase Assay (In Vitro Functional Assay)

Cells stably expressing the rat NPY5 receptor are resuspended in serum-free DMEM
 5 containing 10 mM HEPES (pH 7.4) and 1 mM isobutylmethylxanthine (IBMX). 1 μ M forskolin and drug dilution are then added to the cells. After a 20 minute incubation of the samples at 37°C, the assay is stopped by placing the samples in boiling water for 3 minutes. The cAMP produced in each sample is quantitated with a radioimmunoassay kit (NEN DuPont). Data are expressed as a percentage of forskolin-stimulated adenylate cyclase. The
 10 results of compounds tested according to this protocol are reported in Table 3.

TABLE 3

Composition	hNPY1	hNPY2	hNPY4	hNPY5	rNPY5	rNPY5
	IC50	IC50	IC50	IC50	IC50	%FSAC (10 μ M)
	(μ M)	(μ M)	(μ M)	(μ M)	(μ M)	(μ M)
1	>5	>10	>5	0.64	95*	ND
2	>5	>5	>5	>10	>10	ND
3	>5	>5	>5	0.16	0.12	103
4	>5	>5	>5	0.34	0.36	ND
5	ND	>5	>5	ND	>1	ND
6	>5	>5	>5	0.16	0.18	ND
7	>5	>5	>5	1.6	0.44	ND
8	>5	>5	>5	0.16	0.029	99
9	ND	>5	ND	0.44	93*	ND
10	ND	>5	ND	0.1	97*	ND
11	ND	>5	ND	0.5	95*	ND
12	ND	>5	ND	0.48	95*	ND
13	ND	>5	ND	5.6	71*	ND
14	ND	>5	ND	>10	51*	ND
15	ND	>5	ND	9.8	66*	ND
16	ND	>5	ND	3.6	80*	ND
17	ND	>5	ND	0.38	ND	ND
18	ND	>5	ND	0.2	ND	ND
19	ND	>5	ND	0.71	ND	ND
20	ND	>5	ND	0.42	ND	ND
21	ND	>5	ND	0.43	ND	ND
22	ND	>5	ND	0.31	ND	ND

Composition	hNPY1	hNPY2	hNPY4	hNPY5	rNPY5	rNPY5
	IC50	IC50	IC50	IC50	IC50	%FSAC (10 μ M)
	(μ M)	(μ M)	(μ M)	(μ M)	(μ M)	(μ M)
23	ND	>5	ND	>10	ND	ND
24	ND	>5	ND	>10	ND	ND
25	ND	>5	ND	>10	ND	ND
26	ND	>5	ND	>10	ND	ND
27	ND	>5	ND	9	ND	ND
28	ND	>5	ND	>10	ND	ND
29	ND	>5	ND	0.19	ND	ND
30	ND	>5	ND	0.48	ND	ND
31	ND	>5	ND	0.64	ND	ND
32	ND	>5	ND	1.2	ND	ND
33	ND	>5	ND	0.069	ND	ND
34	ND	>5	ND	0.144	ND	ND
35	ND	>5	ND	3.6	ND	ND
36	ND	>5	ND	0.11	ND	ND
37	ND	>5	ND	1.7	ND	ND
38	ND	>5	ND	>10	ND	ND
39	ND	>5	ND	0.49	ND	ND
40	ND	>5	ND	0.69	ND	ND
41	ND	>5	ND	0.33	ND	ND
42	ND	>5	ND	1.5	ND	ND
43	ND	>5	ND	1.3	ND	ND
44	ND	>5	ND	0.32	ND	ND
45	ND	>5	ND	0.17	ND	ND
46	ND	>5	ND	0.3	ND	ND
47	ND	>5	ND	3.8	ND	ND
48	ND	>5	ND	3	ND	ND
49	ND	>5	ND	1.6	ND	ND
50	ND	>5	ND	0.053	ND	ND
51	ND	>5	ND	0.22	ND	105
52	ND	>5	ND	0.73	ND	ND
53	ND	>5	ND	0.21	ND	ND
54	ND	>5	ND	2	ND	ND
55	ND	>5	ND	1.7	ND	ND
56	ND	>5	ND	0.73	ND	ND
57	ND	>5	ND	>1	ND	ND
58	ND	>5	ND	>1	ND	ND
59	ND	>5	ND	>1	ND	ND
60	ND	>5	ND	2.1	ND	ND
61	ND	>5	ND	0.51	ND	ND
62	ND	>5	ND	0.3	ND	ND
63	ND	>5	ND	0.65	ND	ND
64	ND	>5	ND	2.7	ND	ND
65	ND	>5	ND	0.97	ND	ND

Composition	hNPY1	hNPY2	hNPY4	hNPY5	rNPY5	rNPY5
	IC50	IC50	IC50	IC50	IC50	%FSAC (10 μ M)
	(μ M)	(μ M)	(μ M)	(μ M)	(μ M)	(μ M)
66	ND	>5	ND	1.7	ND	ND
67	ND	>5	ND	7.6	ND	ND
68	ND	>5	ND	5	ND	ND
69	ND	>5	ND	6.8	ND	ND
70	ND	>5	ND	>10	ND	ND
71	ND	>5	ND	1.3	ND	ND
72	ND	>5	ND	8.4	ND	ND
73	ND	ND	ND	>1	ND	ND
74	ND	ND	ND	>1	ND	ND
75	ND	ND	ND	>1	ND	ND
76	ND	ND	ND	>1	ND	ND
77	ND	ND	ND	>1	ND	ND
78	ND	ND	ND	>1	ND	ND
79	ND	ND	ND	>1	ND	ND
80	ND	ND	ND	>1	ND	ND
81	ND	ND	ND	ND	>1	ND
82	ND	ND	ND	ND	>1	ND
83	ND	ND	ND	0.21	0.2	ND
84	ND	ND	ND	ND	>1	ND
85	ND	ND	ND	0.2	0.22	ND
86	ND	ND	ND	0.17	0.15	ND
87	ND	ND	ND	0.1	0.12	ND
88	ND	ND	ND	ND	>1	ND
89	ND	ND	ND	0.59	0.72	ND
90	ND	ND	ND	0.26	0.34	ND
91	ND	ND	ND	0.08	0.084	ND
92	ND	ND	ND	0.081	0.072	ND
93	ND	ND	ND	ND	>1	ND
94	ND	ND	ND	0.67	1.2	ND
95	ND	ND	ND	ND	>1	ND
96	ND	ND	ND	0.85	0.61	ND
97	ND	ND	ND	0.11	0.09	ND
98	ND	ND	ND	0.32	0.29	ND
99	ND	ND	ND	0.69	0.51	ND
100	ND	ND	ND	ND	>1	ND
101	ND	ND	ND	1.4	1.5	ND
102	ND	ND	ND	0.34	0.31	ND
103	ND	ND	ND	ND	>1	ND
104	ND	ND	ND	ND	>1	ND
105	ND	ND	ND	ND	>1	ND
106	ND	ND	ND	ND	>1	ND
107	ND	ND	ND	ND	>1	ND
108	ND	ND	ND	ND	>1	ND

Composition	hNPY1	hNPY2	hNPY4	hNPY5	rNPY5	rNPY5
	IC50	IC50	IC50	IC50	IC50	%FSAC (10 μ M)
	(μ M)	(μ M)	(μ M)	(μ M)	(μ M)	(μ M)
109	ND	ND	ND	0.61	0.37	ND
110	ND	ND	ND	0.29	0.34	ND
111	ND	ND	ND	1.4	0.57	ND
112	ND	ND	ND	ND	>1	ND
113	ND	ND	ND	ND	>1	ND
114	ND	ND	ND	0.9	0.39	ND
115	ND	ND	ND	0.9	0.36	ND
116	ND	ND	ND	1.3	2	ND
117	ND	ND	ND	ND	>1	ND
118	ND	ND	ND	ND	>1	ND
119	ND	ND	ND	0.63	1.5	ND
120	ND	ND	ND	1.3	0.53	ND
121	ND	ND	ND	0.91	2.8	ND
122	ND	ND	ND	1.5	>1	ND
123	ND	ND	ND	0.42	0.53	ND
124	ND	ND	ND	>1	2.3	ND
125	ND	ND	ND	1	0.36	ND
126	ND	ND	ND	ND	>1	ND
127	ND	ND	ND	0.059	0.05	ND
128	ND	ND	ND	ND	>1	ND
129	ND	ND	ND	ND	>1	ND
130	ND	ND	ND	0.16	0.15	ND
131	ND	ND	ND	ND	>1	ND
132	ND	ND	ND	ND	>1	ND
133	ND	ND	ND	ND	>1	ND
134	ND	ND	ND	ND	>1	ND
135	ND	ND	ND	ND	>1	ND
136	ND	>5	ND	0.11	95*	ND
137	>5	>5	>5	>10	>10	ND
138	>5	>5	>5	>10	52*	ND
139	>5	>5	>5	>10	>10	ND
140	>5	>5	>5	>10	61*	ND
141	>5	>5	>5	3	3	ND
142	>5	>5	>5	>10	>10	ND
143	>5	>5	>5	3.1	3.9	ND
144	>5	>5	>5	1.2	1.4	ND
145	>5	>5	>5	>10	>10	ND
146	>5	>5	>5	>10	>10	ND
147	>5	>5	>5	>10	>10	ND
148	>5	>5	>5	4	2.4	ND
149	ND	ND	ND	ND	ND	ND
150	>5	ND	>5	>10	>10	ND
151	>5	>5	>5	0.24	0.28	ND

Composition	hNPY1	hNPY2	hNPY4	hNPY5	rNPY5	rNPY5
	IC50	IC50	IC50	IC50	IC50	%FSAC (10μM)
	(μM)	(μM)	(μM)	(μM)	(μM)	(μM)
152	>5	>5	>5	>10	>10	ND
153	>5	ND	>5	>10	>10	ND
154	>5	>5	>5	>10	10	ND
155	>5	>5	>5	>10	>10	ND
156	>5	>5	>5	>10	>10	ND
157	>5	ND	>5	>10	>10	ND
158	>5	ND	>5	>10	>10	ND
159	>5	ND	>5	>10	>10	ND
160	>5	ND	>5	>10	>10	ND
161	>5	ND	>5	>10	>10	ND
162	>5	ND	>5	>10	>10	ND
163	>5	ND	>5	>10	>10	ND
164	>5	ND	>5	1.6	1.7	ND
165	>5	ND	>5	>10	>10	ND
166	>5	ND	>5	>10	>10	ND
167	>5	ND	>5	>10	>10	ND
168	>5	ND	>5	>10	>10	ND
169	>5	ND	>5	>10	>10	ND
170	>5	ND	>5	>10	>10	ND
171	>5	ND	>5	0.553	0.525	ND
172	>5	ND	>5	2.3	2	ND
173	>5	ND	>5	0.08	0.073	ND
174	>5	ND	>5	>10	>10	ND
175	>5	>5	>5	7	ND	ND
176	>5	>5	>5	3	ND	ND
177	ND	>5	>5	>10	ND	ND
178	ND	>5	>5	>10	ND	ND
179	ND	>5	>5	>10	ND	ND
180	ND	>5	>5	>10	ND	ND
181	ND	>5	>5	>10	ND	ND
182	>5	>5	>5	0.87	0.76	ND
183	ND	>5	>5	1.3	1.2	ND
184	ND	ND	ND	ND	ND	ND
185	ND	ND	ND	ND	ND	ND
186	ND	ND	ND	ND	ND	ND
187	>5	>5	>5	>10	>10	ND
188	ND	ND	ND	ND	ND	ND

* percent inhibition at 10μM.

Compounds 137 - 188, each tested according to one or more assays set forth in this

Example are known compounds. The name of each known compound and its source is set

5 forth in Table 4 immediately below.

TABLE 4

Composition	Name	Reference
137	N-(4-Chloro-phenyl)-2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylsulfanyl)-acetamide	MAYBRIDGE SPB 02423
138	N-(4-Chloro-phenyl)-2-[4-methyl-5-(2-methyl-thiazol-4-yl)-4H-[1,2,4]triazol-3-ylsulfanyl]-acetamide	MAYBRIDGE SPB 02442
139	N-(4-Chloro-phenyl)-2-(1-methyl-1H-imidazol-2-ylsulfanyl)-acetamide	MAYBRIDGE SPB 02459
140	N-(4-Chloro-phenyl)-2-(1-ethyl-1H-benzoimidazol-2-ylsulfanyl)-acetamide	MAYBRIDGE SPB 02616
141	2-[4-(3-Fluoro-phenyl)-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-ylsulfanyl]-N-(4-isopropyl-phenyl)-acetamide	MAYBRIDGE SPB 02164
142	N-(4-Chloro-phenyl)-2-[4-methyl-5-(3-methyl-2-methylsulfanyl-3H-imidazol-4-yl)-4H-[1,2,4]triazol-3-ylsulfanyl]-acetamide	MAYBRIDGE KM 07084
143	N-(4-tert-Butyl-phenyl)-2-(1-methyl-1H-imidazol-2-ylsulfanyl)-acetamide	MAYBRIDGE XAX 00073
144	2-(1-Methyl-1H-tetrazol-5-ylsulfanyl)-N-(4-trifluoromethoxy-phenyl)-acetamide	MAYBRIDGE NRB 00231
145	N-(4-Iodo-phenyl)-2-(1-methyl-1H-imidazol-2-ylsulfanyl)-acetamide	MAYBRIDGE NRB 00039
146	N-(4-Fluoro-phenyl)-2-(1-methyl-4,5-dihydro-1H-imidazol-2-ylsulfanyl)-acetamide	MAYBRIDGE NRB 00023
147	N-(4-Chloro-phenyl)-2-[4-(3-fluoro-phenyl)-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-ylsulfanyl]-acetamide	MAYBRIDGE SPB 02166
148	N-(4-sec-Butyl-phenyl)-2-(1-methyl-1H-imidazol-2-ylsulfanyl)-acetamide	G & J JS179
149	N-(4-Butyl-phenyl)-2-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetamide	G & J JS415
150	2-[4-Methyl-5-(5-methyl-isoxazol-3-yl)-4H-[1,2,4]triazol-3-ylsulfanyl]-N-phenyl-acetamide	MAYBRIDGE SPB 06306
151	N-(3-Cyano-phenyl)-2-p-tolylsulfanyl-acetamide	MAYBRIDGE BTB 02777
152	2-[4-Methyl-5-(3-oxo-6-trifluoromethyl-2,3-dihydro-benzo[1,4]thiazin-4-ylmethyl)-4H-[1,2,4]triazol-3-ylsulfanyl]-N-phenyl-acetamide	MAYBRIDGE KM 08376
153	N-(4-Isopropyl-phenyl)-2-[4-methyl-5-(thiophen-2-ylsulfanylmethyl)-4H-[1,2,4]triazol-3-ylsulfanyl]-acetamide	MAYBRIDGE KM 04673
154	N-(4-Chloro-phenyl)-2-[5-(4-chloro-phenyl)-1-methyl-1H-imidazol-2-ylsulfanyl]-acetamide	MAYBRIDGE SPB 02397
155	N-(4-Isopropyl-phenyl)-2-(1-methyl-1H-imidazol-2-ylsulfanyl)-acetamide	MAYBRIDGE SPB 02458
156	N-(4-Ethoxy-phenyl)-2-(1-methyl-1H-imidazol-2-ylsulfanyl)-acetamide	G & J JS438
157	N-(2-Methoxy-5-methyl-phenyl)-2-(4-methyl-5-trifluoromethyl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetamide	MAYBRIDGE NRB 04679

Composition	Name	Reference
158	N-(4-Isopropyl-phenyl)-2-(4-methyl-5-thiophen-3-ylmethyl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetamide	MAYBRIDGE SPB 02379
159	N-(4-Chloro-phenyl)-2-[4-methyl-5-(3-methylsulfanyl-6,7-dihydro-benzo[c]thiophen-1-yl)-4H-[1,2,4]triazol-3-ylsulfanyl]-acetamide	MAYBRIDGE KM 04947
160	N-(4-Chloro-phenyl)-2-[5-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl]-acetamide	MAYBRIDGE SPB 05815
161	N-(4-Chloro-phenyl)-2-[5-(4-chloro-phenyl)-4-(2,2-dimethoxy-ethyl)-4H-[1,2,4]triazol-3-ylsulfanyl]-acetamide	MAYBRIDGE SPB 04886
162	N-(4-Chloro-phenyl)-2-[4-(2,2-dimethoxy-ethyl)-5-phenyl-4H-[1,2,4]triazol-3-ylsulfanyl]-acetamide	MAYBRIDGE SPB 04875
163	2-[4-(2,2-Dimethoxy-ethyl)-5-phenyl-4H-[1,2,4]triazol-3-ylsulfanyl]-N-(4-isopropyl-phenyl)-acetamide	MAYBRIDGE SPB 04867
164	N-(4-tert-Butyl-phenyl)-2-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetamide	MAYBRIDGE XAX 00070
165	N-(4-Isopropyl-phenyl)-2-(1-isopropyl-5-trifluoromethyl-1H-benzimidazol-2-ylsulfanyl)-acetamide	MAYBRIDGE SPB 02565
166	2-[5-(4-Chloro-phenyl)-4-(2,2-dimethoxy-ethyl)-4H-[1,2,4]triazol-3-ylsulfanyl]-N-(4-isopropyl-phenyl)-acetamide	MAYBRIDGE SPB 04888
167	N-(4-Chloro-phenyl)-2-[4-methyl-5-(3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-2-ylmethyl)-4H-[1,2,4]triazol-3-ylsulfanyl]-acetamide	MAYBRIDGE KM 07504
168	N-(4-Chloro-phenyl)-2-(4-methyl-5-thiophen-3-ylmethyl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetamide	MAYBRIDGE SPB 02380
169	N-(4-Chloro-phenyl)-2-[4-methyl-5-[4-methyl-2-(5-methyl-isoxazol-3-yl)-thiazolidin-5-yl]-4H-[1,2,4]triazol-3-ylsulfanyl]-acetamide	MAYBRIDGE SPB 05325
170	N-(4-Fluoro-phenyl)-2-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetamide	G & J JS646
171	N-(4-sec-Butyl-phenyl)-2-(1-methyl-1H-tetrazol-5-ylsulfanyl)-acetamide	G & J JS165
172	N-(4-sec-Butyl-phenyl)-2-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetamide	G & J JS169
173	N-(4-Cyclohexyl-phenyl)-2-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetamide	G & J JS020
174	2-(4-Methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-p-tolyl-acetamide	G & J JS087
175	N-(4-Chloro-phenyl)-2-[4-methyl-5-(2-oxo-5-trifluoromethyl-2H-pyridin-1-ylmethyl)-4H-[1,2,4]triazol-3-ylsulfanyl]-acetamide	MAYBRIDGE SPB 06531
176	N-(4-Isopropyl-phenyl)-2-[4-methyl-5-(2-oxo-5-trifluoromethyl-2H-pyridin-1-ylmethyl)-4H-[1,2,4]triazol-3-ylsulfanyl]-acetamide	MAYBRIDGE SPB 06687

Composition	Name	Reference
177	N-(4-Isopropyl-phenyl)-2-{4-methyl-5-[4-methyl-2-(5-methyl-isoxazol-3-yl)-thiazol-5-yl]-4H-[1,2,4]triazol-3-ylsulfanyl}-acetamide	MAYBRIDGE SPB 05324
178	N-(4-Chloro-phenyl)-2-[4-(2-trifluoromethyl-phenyl)-5-undecyl-4H-[1,2,4]triazol-3-ylsulfanyl]-acetamide	MAYBRIDGE SPB 02432
179	N-(4-Isopropyl-phenyl)-2-[4-(2-trifluoromethyl-phenyl)-5-undecyl-4H-[1,2,4]triazol-3-ylsulfanyl]-acetamide	MAYBRIDGE SPB 02433
180	N-(4-Chloro-phenyl)-2-(1-isopropyl-5-trifluoromethyl-1H-benzimidazol-2-ylsulfanyl)-acetamide	MAYBRIDGE SPB 02567
181	N-(4-Chloro-phenyl)-2-(5-hydroxy-4-pentyl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetamide	MAYBRIDGE SPB 02154
182	N-(4-Cyclohexyl-phenyl)-2-(pyridin-2-ylsulfanyl)-acetamide	MAYBRIDGE NRB 00156
183	N-(4-Cyclohexyl-phenyl)-2-p-tolylsulfanyl-acetamide	MAYBRIDGE NRB 00155
184	2-(4-Bromo-phenylsulfanyl)-N-(4-cyclohexyl-phenyl)-acetamide	G & J JS016
185	2-(4-Chloro-phenylsulfanyl)-N-(4-cyclohexyl-phenyl)-acetamide	G & J JS377
186	N-(4-Cyclohexyl-phenyl)-2-hydrazinocarbonylmethylsulfanyl-acetamide	MAYBRIDGE NRB 00159
187	N-(4-Chloro-phenyl)-2-(4,5-dihydro-1H-imidazol-2-ylsulfanyl)-acetamide	Indian J. Chem., Section B 1982, 21B, 4-7.
188	N-(4-Cyclohexyl-phenyl)-2-m-tolylsulfanyl-acetamide	G & J JS375

EXAMPLE 5

This example describes the preparation of a tablet that includes composition 1 as
5 prepared in Example 2.

Formulation of a coated tablet according to the invention

Each tablet contains:

Compound 1 of Example 2	583.0 mg
Microcrystalline cellulose	55.0 mg
10 Corn starch	72.0 mg
Poly(1-vinyl-2-pyrrolidone)	30.0 mg
Highly dispersed silica	5.0 mg
Magnesium stearate	5.0 mg
15 Total	750.0 mg

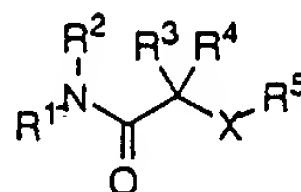
The tablet coating contains:

	Poly(O-hydroxypropyl O-methyl)-cellulose 15 cp	6.0 mg
	Macrogol 4000 rec. INN	2.0 mg
5	(polyethylene glycol DAB)	2.0 mg
	Titanium(IV) oxide	10.0 mg

While the present invention has been described by means of specific embodiments, it will be understood that modifications may be made without departing from the spirit of the invention. The scope of the invention is not to be considered as limited by the description of the invention set forth in the specification and examples.

What we claim is:

1. A method for treating mammalian disorders mediated by the NPY Y5 receptor comprising administering to the mammal a therapeutically effective amount of at least one compound having the formula:



5

or pharmaceutically acceptable salts thereof wherein R_1 - R_5 are each individually selected from the group of substituents including hydrogen, halogen, hydroxyl, thiol, lower alkyl, substituted lower alkyl, alkenyl, alkynyl, alkylalkenyl, alkyl alkynyl, alkoxy, alkylthio, acyl, aryloxy, amino, amido, carboxyl, aryl, substituted aryl, heterocycle, heteroaryl, substituted heterocycle, heteroalkyl, cycloalkyl, substituted cycloalkyl, alkylcycloalkyl, alkylcycloheteroalkyl, phenyl, substituted phenyl, benzothiophene, furan, fluoride, nitro, cyano, naphthyl, substituted naphthyl, fluorene, substituted fluorene and dibenzofuran, and wherein X is oxygen or sulfur.

2. The method according to claim 1 wherein R^1 is selected from the group of substituents including lower alkyl, substituted lower alkyl, substituted phenyl, phenyl, benzothiophene, furan, naphthyl, substituted naphthyl, fluorene, substituted fluorene, dibenzofuran and fluorine.

3. The method according to claim 1 wherein R^1 is: phenyl that is substituted with one or more substituents including phenyl, cyanophenyl, halogens including fluoride, chloride, iodide, and bromide, thiophene, perfluoroalkyl, cyclohexyl, alkoxy, benzoyl, a branched or straight chain alkyl group having from 1 to 6 or more carbon atoms; naphthyl; substituted naphthyl; fluorene; substituted fluorene; and dibenzofuran.

4. The method according to claim 1 wherein R^2 is selected from the group hydrogen, an unsubstituted alkyl having from 1 to 6 carbon atoms, and a substituted alkyl wherein the alkyl group has from 1 to 6 carbon atoms.

5. The method according to claim 1 wherein R^3 and R^4 are each individually
5 selected from the group hydrogen, lower alkyl, substituted lower alkyl, and phenyl.

6. The method according to claim 5 wherein R^3 and R^4 are each individually selected from hydrogen, $-CH_3$, unsubstituted phenyl, and from phenyl that is substituted with halogen, with an alkoxy having from 1 to 6 carbon atom, and with an alkyl group having from 1 to 6 carbon atoms.

10 7. The method of claim 1 wherein R^1 and R^2 taken together with an adjacent nitrogen atom form a 3 to 7 atom heterocycle.

8. The method according to claim 1 wherein R^5 is: a lower alkyl; a substituted lower alkyl wherein the substituted lower alkyl may be substituted with one or more substituents selected from the group including hydroxyl, mercaptomethylphenyl, furan, and
15 phenyl substituted up to three times with a methyl group; N-methylpiperidine; phenyl optionally substituted with a lower alkyl group, alkoxy, thioalkoxy, amino, aminoacyl, hydroxyl or fluoro group; pyridine; pyridine N-oxide; unsubstituted pyrimidine; pyrimidine substituted with from one to three substituents selected from the group including lower alkyl, hydroxyl, nitroso, amino, trifluoromethyl, and thiol; 1,3,5-triazine substituted up to
20 two times with amino, thiol, or a mixture thereof; 4,5-dihydrothiazole; phenyl substituted 1,2,4-oxadiazole; 1,3,4-oxadiazole substituted with phenyl or with 2,4-dichlorophenoxyethyl; 1,3,4-thiadiazole substituted with amino, an aminoalkyl group having from 1 to 6 carbon atoms, and with lower alkyl; unsubstituted imidazole; imidazole that is substituted with one or more substituents including lower alkyl, phenyl, chloride

substituted phenyl, hydroxymethyl, carboalkoxy, and mixtures thereof; 4,5-dihydroimidazole; lower alkyl substituted 4, 5-dihydroimidazole; 1,2,4-triazole; 1, 2, 4-triazole that is mono-substituted or bi-substituted with lower alkyl, unsubstituted thiazole, thiazole that is mono-substituted or bi-substituted with lower alkyl or 5-methylisoxazole
5 thereof, lower alkyl substituted isoxazole, furan, unsubstituted imidazole, imidazole that is substituted with one or more substituents including lower alkyl, thioalkoxy, thiophenylsulfanylmethyl, thiophenylmethyl, 4-methyl-5-(3-methylsulfanyl-6; 7-dihydrobenzo[c]thiophene), unsubstituted pyridine, pyridine that is substituted with one or more substituents including alkoxy, chloride, trifluoromethyl or mixtures thereof, amino,
10 trifluoromethyl, unsubstituted phenyl, phenyl that is substituted with alkoxy, chloride, trifluoromethyl and mixtures thereof, 2, 2-dimethoxyethyl, 2-oxo-5-trifluoromethyl-2H-pyridin-1-methyl or hydroxy; 3-fluorophenyl substituted 5-oxo-1, 2, 4 triazole; unsubstituted tetrazole; tetrazole substituted with lower alkyl, phenyl, or hydroxy substituted phenyl; unsubstituted benzoimidazole; benzoimidazole that is substituted with
15 one or more substituents including lower alkyl, alkoxy, nitro, trifluoromethyl, and mixtures thereof; unsubstituted benzothiazole; benzothiazole that is substituted with alkoxy or chloride; benzooxazole; unsubstituted pyrazolo[3,4-d]pyrimidin; amine substituted pyrazolo[3,4-d]pyrimidin; 1,2,4-triazolo[1,5a]pyrimidine; amine substituted 1,2,4-triazolo[1,5a]pyrimidine; 1,2,4-triazolo[1,5a]pyrimidine bi-substituted with unsubstituted or
20 substituted lower alkyl or bi-substituted with unsubstituted or substituted pyridine that when substituted is mono- or bi-substituted with amine, hydroxy, 3, 4-dihydroxy-5-hydroxymethyltetrahydrofuran, or mixtures thereof; 4-oxo-3, 4-dihydroquinazoline; quinazoline; quinoline; and trifluoromethyl substituted quinoline.

9. The method according to claim 1 wherein the pharmaceutical result is selected from obesity and eating disorders.

10. The method according to claim 9 wherein the mammal is a human and the eating disorder is selected from the group consisting of bulimia and obesity.

5 11. The method according to claim 1 wherein the pharmaceutical result is the treatment of obesity related disorders.

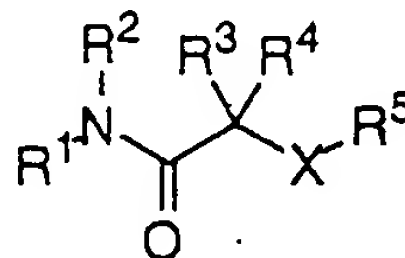
12. The method according to claim 1 wherein the mammal is a human.

13. The method according to claim 1 wherein the therapeutically effective amount ranges from about 0.001 to about 100 mg/kg weight of the mammal.

10 14. The method according to claim 1 wherein the composition is administered orally in the form of a solution.

15. The method according to claim 1 wherein the composition is administered orally in the form of a tablet.

16. A composition of matter having the formula:



15

or pharmaceutically acceptable salts thereof wherein R¹-R⁵ are each individually selected from the group of substituents including hydrogen, halogen, hydroxyl, thiol, lower alkyl, substituted lower alkyl, alkenyl, alkynyl, alkylalkenyl, alkyl alkynyl, alkoxy, alkylthio, acyl, aryloxy, amino, amido, carboxyl, aryl, substituted aryl, heterocycle, heteroaryl, substituted heterocycle, heteroalkyl, cycloalkyl, substituted cycloalkyl, alkylcycloalkyl, alkylcycloheteroalkyl, nitro, or cyano, X is oxygen or sulfur, except that R¹ is not any

20

compound that is used in the R¹ position of compounds 137-188 of Table 4.

17. The composition of claim wherein R¹ is selected from the group of substituents including lower alkyl, substituted lower alkyl, substituted phenyl, phenyl, benzothiophene, furan naphthyl, substituted naphthyl, fluorene, substituted fluorene, 5 dibenzofuran, and fluorine.

18. The composition of claim 16 wherein R¹ is: phenyl that is mono-substituted or bi-substituted with one or more substituents including phenyl, cyanophenyl, halogens including fluoride, chloride, and bromide, thiophene, perfluoroalkyl, cyclohexyl, alkoxy, benzoyl, iodide, a branched or straight chain alkyl group having from 1 to 6 or more carbon 10 atoms; naphthyl; substituted naphthyl; fluorene; substituted fluorene; and dibenzofuran.

19. The composition according to claim 16 wherein R³ and R⁴ are each individually selected from the group hydrogen, lower alkyl, substituted lower alkyl, and phenyl.

20. The composition according to claim 16 wherein R³ and R⁴ are each 15 individually selected from hydrogen, -CH₃, unsubstituted phenyl, and from phenyl that is substituted with halogen, with an alkoxy having from 1 to 6 carbon atoms, and with an alkyl group having from 1 to 6 carbon atoms.

21. The composition of claim 16 wherein R¹ and R² taken together with an adjacent nitrogen atom form a 3 to 7 atom heterocycle.

20 22. The composition of claim 16 wherein R⁵ is: a lower alkyl; a substituted lower alkyl wherein the substituted lower alkyl may be substituted with one or more substituents selected from the group including hydroxyl, mercaptomethylphenyl, furan, and phenyl substituted up to three times with a methyl group; N-methylpiperidine; phenyl optionally substituted with a lower alkyl group, alkoxy, thioalkoxy, amino, aminoacyl,

hydroxyl or fluoro group; pyridine; pyridine N-oxide; unsubstituted pyrimidine; pyrimidine substituted with from one to three substituents selected from the group including lower alkyl, hydroxyl, nitroso, amino, trifluoromethyl, and thiol; 1,3,5-triazine substituted up to two times with amino, thiol, or a mixture thereof; 4,5-dihydrothiazole; phenyl substituted
5 1,2,4-oxadiazole; 1,3,4-oxadiazole substituted with phenyl or with 2,4-dichlorophenoxyethyl; 1,3,4-thiadiazole substituted with amino, an aminoalkyl group having from 1 to 6 carbon atoms, and with lower alkyl; unsubstituted imidazole; imidazole that is substituted with one or more substituents including lower alkyl, phenyl, chloride substituted phenyl, hydroxymethyl, carboalkoxy, and mixtures thereof; 4,5-
10 dihydroimidazole; lower alkyl substituted 4, 5-dihydroimidazole; 1,2,4-triazole; 1, 2, 4-triazole that is mono-substituted or bi-substituted with lower alkyl, unsubstituted thiazole, thiazole that is mono-substituted or bi-substituted with lower alkyl or 5-methylisoxazole thereof, lower alkyl substituted isoxazole, furan, unsubstituted imidazole, imidazole that is substituted with one or more substituents including lower alkyl, thioalkoxy,
15 thiophenylsufanylmethyl, thiophenylmethyl, 4-methyl-5-(3-methylsulfanyl-6; 7-dihydrobenzo[c]thiophene), unsubstituted pyridine, pyridine that is substituted with one or more substituents including alkoxy, chloride, trifluoromethyl or mixtures thereof, amino, trifluoromethyl, unsubstituted phenyl, phenyl that is substituted with alkoxy, chloride, trifluoromethyl and mixtures thereof, 2, 2-dimethoxyethyl, 2-oxo-5-trifluoromethyl-2H-
20 pyridin-1-methyl or hydroxy; 3-fluorophenyl substituted 5-oxo-1, 2, 4 triazole; unsubstituted tetrazole; tetrazole substituted with lower alkyl, phenyl, or hydroxy substituted phenyl; unsubstituted benzoimidazole; benzoimidazole that is substituted with one or more substituents including lower alkyl, alkoxy, nitro, trifluoromethyl, and mixtures thereof; unsubstituted benzothiazole; benzothiazole that is substituted with alkoxy or

chloride; benzoxazole; unsubstituted pyrazolo[3,4-d]pyrimidin; amine substituted pyrazolo[3,4-d]pyrimidin; 1,2,4-triazolo[1,5a]pyrimidine; amine substituted 1,2,4-triazolo[1,5a]pyrimidine; 1,2,4-triazolo[1,5a]pyrimidine bi-substituted with unsubstituted or substituted lower alkyl or bi-substituted with unsubstituted or substituted pyridine that when
5 substituted is mono- or bi-substituted with amine, hydroxy, 3, 4-dihydroxy-5-hydroxymethyltetrahydrofuran, or mixtures thereof; 4-oxo-3, 4-dihydroquinazoline; quinazoline; quinoline; and trifluoromethyl substituted quinoline.

23. A pharmaceutical dosage form comprising the composition of claim 16 and at least one additive.

10 24. The pharmaceutical dosage form of claim 23 wherein the pharmaceutical dosage form is administered by a method selected from oral administration, dermal administration, injection, via an implant, by inhalation, intravenously, and by suppository.

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/US 98/02122

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D233/42 C07D239/38 C07D257/04 C07D235/28 C07D473/18
A61K31/415 C07D239/78 C07D277/16 C07D487/04 C07D213/89
C07D263/58 C07D277/72 C07D213/70 C07D285/125 C07D249/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	N. HELLSTRÖM, T. LAURITZSON: "Ueber Alkyl-thioglykolsäure-anilide bzw. -p-toluidide und entsprechende Thionyl-Verbindungen" CHEM. BER., vol. 69, 1936, pages 1999-2003, XP002068963 see tables 1,2	16-22
X	US 2 109 698 A (MONSANTO CHEMICAL COMPANY) 1 March 1938 see claim 25	16-22

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
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T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

25 June 1998

Date of mailing of the international search report

10.07.98

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INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/US 98/02122

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D271/07 C07D307/64

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. E. LAMBLING: "Action de l'isocyanate de phényle sur quelques acides-éthers" BULL. CHEM. SOC. FR, vol. 17, 1897, pages 356-362, XP002068964 see page 357	16-22
X	J. MAAS ET AL.: "The action of diazoacetic ester on pyridone-2" REC. TRAV. CHIM. PAYS-BAS, vol. 74, no. 2, 1955, pages 175-180, XP002068965 see page 179	16-22

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

25 June 1998

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10.07.98

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Herz, C

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US 98/02122

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	L. A. REITER: "A general synthesis of 4(5)-acylimidazoles from 4-acylaminoisoxazoles" TETRAHEDRON LET., vol. 26, no. 29, 1985, pages 3423-3426, XP002068966 see examples 2F,3F	16-22
X	--- S. J. CORNFORTH, T. PENGELLY: "Failure to verify a reported synthesis of the aconitine skeleton" TETRAHEDRON LETT., vol. 23, no. 21, 1982, pages 2213-2216, XP002068967 see page 2213	16-22
X	--- B. R. BAKER, J. A. HURLBUT: "Irreversible enzyme inhibitors. CVII. Proteolytic Enzymes. I. Bulk tolerance within chymotrypsin-inhibitor complexes" J. MED. CHEM., vol. 10, no. 6, 1967, pages 1129-1133, XP002068968 see table IV	16-24
X	--- G. F. DUFFIN, J. D. KENDALL: "Anhyro-compounds from nitrogen-containing derivatives of thioglycollic acid. Part I. Pyridine and Quinoline compounds" J. CHEM. SOC., 1951, pages 734-739, XP002068969 see page 739	16-22
X	--- A. MISRA: "Certain thiazolo-benzimidazoles and thiazino-benzimidazoles" J. ORG. CHEM., vol. 23, 1958, pages 897-899, XP002068970 see page 898	16-22
X	--- P. METZ, C. LINZ: "Claisen rearrangement of N-Silyl Ketene N,O-Acetals Generated from Allyl N-Phenylimidates" TETRAHEDRON, vol. 50, no. 13, 1994, pages 3951-3966, XP002068971 * Compound of formula 13b *	16-22
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INTERNATIONAL SEARCH REPORT

Intern. Application No.

PCT/US 98/02122

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	H. A. EL-SHERIEF ET AL.: "Synthesis of Some New Benzoxazole, Benzthiazole and Benzimidazole Derivatives with Biological Activity" J. INDIAN CHEM. SOC., vol. 60, no. 1, 1983, pages 58-60, XP002041292 see table 1 ---	16-24
X	A. M. MAHMOUD ET AL.: "Synthesis and Biological Activity of Some New 2-(N-Substituted Carboxamidomethyl Thio)-Naphth[1,2-d]Oxazoles - Part V" J. INDIAN CHEM. SOC., vol. 59, no. 5, 1982, pages 675-677, XP002068972 see table 1 ---	16-24
X	H.-G. BOIT: "Beilsteins Handbuch der Organischen Chemie, Viertes Ergänzungswerk, Vierter Band, Erster Teil" 1977, SPRINGER-VERLAG, BERLIN - HEIDELBERG - NEW YORK XP002068973 * 2-Methoxy-N-methyl-acetamid, N-Methyl-2-methylmercapto-acetamid * see page 251 ---	16-22
A	WO 96 40660 A (PFIZER INC.) 19 December 1996 see claims 1-40 ---	16-24
A	WO 96 12490 A (ELI LILLY AND COMPANY) 2 May 1996 see claims 1-8 ---	16-24
A	WO 92 06079 A (PFIZER INC.) 16 April 1992 see claims 1-40 ---	16-24
A	WO 96 12489 A (ELI LILLY AND COMPANY) 2 May 1996 see claims 1-5 ---	16-24
A	EP 0 747 356 A (BRISTOL-MYERS SQUIBB COMPANY) 11 December 1996 see claims 1-10 ---	16-24
A	EP 0 448 765 A (HEUMANN PHARMA GMBH & CO) 2 October 1991 see claims 1-20 -----	16-24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/02122

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-15
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 1-15 are directed to a therapeutical method performed on humans. Under the terms of Rule 39.1 (iv) the International Searching Authority is not required to carry out a search on such claims.
2. ☒ Claims Nos.: 16-24 (part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 98/02122

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 16-24 (part)

In view of the large number of compounds, which are defined by the general definition in the independent claims, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims, and to the general idea underlying the application. (see Guidelines, Chapter III, paragraph 2.3).

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Patent Application No

PCT/US 98/02122

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2109698 A	01-03-1938	US 2171305 A	29-08-1939
WO 9640660 A	19-12-1996	AU 4231996 A	31-05-1996
		AU 5578796 A	30-12-1996
		BR 9509610 A	28-10-1997
		EP 0790989 A	27-08-1997
		EP 0833823 A	08-04-1998
		FI 971931 A	06-05-1997
		NO 972091 A	02-07-1997
		PL 321136 A	24-11-1997
		WO 9614307 A	17-05-1996
WO 9612490 A	02-05-1996	AU 689664 B	02-04-1998
		AU 3895595 A	15-05-1996
		CZ 9701159 A	15-10-1997
		EP 0785785 A	30-07-1997
		FI 971635 A	17-04-1997
		HU 76852 A	29-12-1997
		NO 971520 A	03-04-1997
		US 5567714 A	22-10-1996
		US 5504094 A	02-04-1996
		US 5567715 A	22-10-1996
		US 5576337 A	19-11-1996
WO 9206079 A	16-04-1992	AT 121389 T	15-05-1995
		AU 651145 B	14-07-1994
		AU 8746391 A	28-04-1992
		CA 2089736 A	29-03-1992
		CN 1060285 A	15-04-1992
		CZ 9203874 A	16-02-1994
		DE 69109125 D	24-05-1995
		DE 69109125 T	28-09-1995
		DK 550635 T	04-09-1995
		EP 0550635 A	14-07-1993
		ES 2071334 T	16-06-1995
		FI 931370 A	26-03-1993
		HU 68667 A	28-07-1995
		IE 66042 B	13-12-1995
		JP 7072175 B	02-08-1995
		JP 6501267 T	10-02-1994

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern: a) Application No

PCT/US 98/02122

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9206079 A		PT 99064 A	31-08-1992
		ZA 9107744 A	29-03-1993
WO 9612489 A	02-05-1996	US 5663192 A	02-09-1997
		AU 3953795 A	15-05-1996
		EP 0716854 A	19-06-1996
EP 747356 A	11-12-1996	US 5635503 A	03-06-1997
		AU 5475696 A	19-12-1996
		CA 2178413 A	08-12-1996
		JP 8337570 A	24-12-1996
EP 448765 A	02-10-1991	AT 109979 T	15-09-1994
		AU 637882 B	10-06-1993
		CA 2037433 A	01-10-1991
		DE 59006842 D	22-09-1994
		DK 448765 T	19-09-1994
		IE 65252 B	18-10-1995
		IL 97424 A	26-05-1995
		JP 7089939 A	04-04-1995
		PT 97138 A	29-11-1991